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BRITISH HEART JOURNAL

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In association with the British Cardiac Society

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REFERENCES

1. Study Group, *Europ. Heart J.*, 1987, **8**, 77.
2. Lipid Research Clinics Programme, *J. Amer. med. Ass.*, 1984, **251**, 351-364.
3. Data on file, Merck Sharp & Dohme Limited.

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BRITISH
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VIEWPOINT

Does angioplasty need on site surgical cover? A surgeon's view

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Though angioplasty is an established technique for the management of coronary artery disease, there is still controversy about whether it needs on site surgical cover.

The aims of angioplasty and coronary artery bypass surgery in the management of coronary disease are similar, namely to relieve symptoms and in certain groups to improve prognosis, at the lowest risk and morbidity. Because the development of myocardial damage during both procedures significantly reduces long term survival, treatment strategies must not be based on short term results. Myocardial damage at the time of intervention and subsequently is important.

The principal risk of angioplasty is the development of acute myocardial ischaemia progressing to infarction owing to vessel occlusion with or without dissection. Increasing technical skills and improved equipment may reduce these complications but vessel occlusion is likely to remain the chief immediate complication of angioplasty.

The most reliable data on the true incidence of complications of angioplasty are more likely to come from registers than from individual hospitals. In the United States, the Second Generation 1985/6 Percutaneous Transluminal Coronary Angioplasty Register of the National Heart, Lung and Blood Institute (incorporating 1801 patients) showed a vessel occlusion rate of 4·9%, an emergency coronary artery bypass rate of 3·5%, a non-fatal myocardial infarction rate of 4·3%, and an in-hospital mortality of 1% (varying from 0·2% for single vessel disease to 2·2% for triple vessel disease).[1] The French registry for 1987 reviewed 2700 patients and recorded a 2·1% infarction rate, a 1·7% urgent surgery rate, and 0·9% mortality.[2]

Not all patients in whom vessel occlusion develops need either further angioplasty or emergency surgery, particularly if there is no evidence of myocardial ischaemia or if the occluded vessel is very small. A further group of patients will have been advised to have angioplasty rather than surgery because disease in other organs puts them a higher surgical risk and in such patients a myocardial infarction may be the less dangerous option.

Clearly defined treatment strategies should be developed to prevent or limit myocardial damage once vessel occlusion occurs and there is evidence of myocardial ischaemia. Prompt action is required and the best solution is one achieved immediately by the angioplasty operator—but such attempts are successful in only about 50% of patients and are still associated with a considerable risk of myocardial infarction. More extended use of techniques such as autoperfusion dilatation catheters, stents, laser welding, or arthrectomy devices[3] might reduce the need for emergency surgery, but they remain experimental. For patients who are haemodynamically unstable, the use of an intra-aortic balloon pump or percutaneous cardiopulmonary bypass may help to stabilise their condition but should not delay surgical intervention.

Given that surgery is important in the mangement of complications of angioplasty, how close should the operating theatre be to the catheterisation laboratory? It is important to plan for the worst outcome—which is cardiac arrest requiring continuing cardiopulmonary resuscitation. Once vessel occlusion and myocardial ischaemia have occurred and it is clear that further angioplasty techniques have failed, most patients should be transferred to the operating theatre as soon as possible. The effect of the length of the interval from occlusion to surgical revascularisation on subsequent infarction is not clear, largely because it is a non-homogeneous population; however, in large series rates of myocardial infarction in patients requiring emergency surgery varied from 11% to 46%.[4] Furthermore, the extent of the infarction as well as its occurrence is important and the evidence of the effects of time to reperfusion from studies of thrombolysis indicates the need for rapid intervention.

In a series of 4142 patients in Eindhoven of whom 155 required emergency surgery, five were taken to theatre in cardiac arrest and 19 in cardiogenic shock and were revascularised in a median time of 103 minutes and the remaining patients in a median time of 135 minutes.[5] Despite this rapid response time, 40% of both groups sustained a myocardial infarction. After a careful analysis the Eindhoven workers concluded that the complications of angioplasty remain unpredictable and they recommended continuing surgical cover.

Richardson *et al* reported on a selected series of 540 angioplasties from Belfast in which 12 patients required urgent surgery and were transferred 2·4 km to another hospital. The mean time to revascularisation was 268 minutes, similar to the time achieved in the receiving hospital.[6] Such intervals are twice as long as in the Eindhoven study and most would view them as being unacceptably long. No information was given on the myocardial infarction rate in the surgical patients and in those who developed vessel occlusion but did not undergo surgery. The absence of these data seriously compromises the value of this study.

Prompt revascularisation can best be achieved in hospitals in which there are at least two operating theatres devoted entirely to cardiac surgery. Then emergencies can be handled quickly without seriously interrupting planned operations.

The earlier the patient reaches the theatre the greater the chance that the surgeon will use the internal mammary artery, which in the territory of the anterior descending coronary artery gives a better long term outcome.

Transfer of the patient to another hospital causes inevitable delay even with coordinated planning. A special report of a Joint American College of Cardiology and American Heart Association Task Force recommended that angioplasty should be undertaken at a hospital where an experienced cardiac surgical team was available for emergency surgery.[7] This is also the view of the Society of Cardiothoracic Surgeons of Great Britain and Ireland and the International Society and Federation of Cardiology.[8] In the United Kingdom there is no agreed policy on this issue and several units are undertaking angioplasty without on site surgical cover. All these units have or could develop close links with a major centre with surgical facilities.

Surely the best option is for the major centres to provide an angioplasty facility for cardiologists who do not have on site surgical cover but who do have the appropriate expertise and experience to undertake angioplasty? Such a policy should improve the results of angioplasty because it would concentrate practitioners of angioplasty into a limited number of hospitals and so increase their opportunities to interchange experience, increase contact with surgeons, and lead to a more comprehensive examination of the place of angioplasty and surgery in the management of coronary artery disease including the role of surgery in myocardial ischaemia induced by angioplasty.

It is more appropriate for cardiologists to travel by car than for patients with acute myocardial ischaemia (who perhaps will require cardiopulmonary resuscitation) to travel by ambulance. Angioplasty supported by on site surgical facilities is the correct policy for the early 1990s and perhaps cardiologists should ask themselves where they as patients would prefer to have an angioplasty.

1 Holmes DR, Holubkov R, Vlietstra RE, *et al*. Comparison of complications during percutaneous transluminal coronary angioplasty from 1977–1981 and from 1985–1986: The National Heart, Lung and Blood Institute Percutaneous Transluminal Coronary Angioplasty Registry. *J Am Coll Cardiol* 1988;**12**:1149–55.

2 Gaspard PL, Didier B, Marco J, *et al*. What can we expect after coronary angioplasty? Immediate results: The French registry. *Eur Heart J* 1989;**10** (abstract suppl): 368.

3 Topol EJ. Emerging strategies for failed percutaneous transluminal coronary angioplasty. *Am J Cardiol* 1989;**63**: 249–50.

4 Talley JD, Jones EL, Weinstraub WS, King SB III. Coronary artery bypass surgery after failed elective percutaneous transluminal coronary angioplasty—a status report. *Circulation* 1989;**79**(suppl I):I.126–I.31.

5 Bredee JJ, Bavinck JH, Berreklouw E, *et al*. Acute myocardial ischaemia and cardiogenic shock after percutaneous transluminal coronary angioplasty; risk factors for and results of emergency coronary bypass. *Eur Heart J* 1989; **10**(suppl H):104–11.

6 Richardson SG, Morton P, Murtagh JG, O'Keeffe DB, Murphy P, Scott ME. Management of acute occlusion during percutaneous transluminal coronary angioplasty: experience of complications in a hospital without on site facilities for cardiac surgery. *Br Med J* 1990;**300**:355–8.

7 A Report of the American College of Cardiology/American Heart Association Task Force on Assessment of Diagnostic and Therapeutic Cardiovascular Procedures (Subcommittee on Percutaneous Transluminal Coronary Angioplasty. Guidelines for percutaneous transluminal coronary angioplasty. *Circulation* 1988;**78**:486–502.

8 Report of the Joint International Society and Federation of Cardiology/World Health Organisation Task Force in Coronary Angioplasty. *Eur Heart J* 1989;**9**:1034–45.

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VIEWPOINT

Does angioplasty need on site surgical cover? A physician's view

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In Europe, including the United Kingdom, many cardiac laboratories perform coronary angioplasty without having on site facilities for surgery. They use a rapidly accessible surgical unit nearby for back up in the event of occlusion. This system was developed as a pragmatic response to balloon dilatation—a revolutionary change in the treatment of coronary disease that was based on angiography skills and facilities. It seemed a reasonable arrangement because Gruentzig and the pioneers of angioplasty had indicated that back up surgery should be provided within 90–120 minutes.

The justification for continuing angioplasty with nearby off site surgery is the results obtained. Richardson *et al* reported that in Belfast the unit with off site surgery provided revascularisation for patients slightly sooner than the unit with on site surgery.[1] None of the 12 patients who had off site surgery died. At the Western General Hospital in Edinburgh our operating theatre for cardiac surgery is three miles away from the catheterisation laboratory.[2] Of 407 angioplasties carried out up to 1989, seven patients had emergency coronary surgery. One, with a main stem dissection, died after operation. Of the six others, three have good left ventricular function and three have moderate function. All are in New York Heart Association symptom class I or II after surgery. The angioplasty mortality was 0·25%. These results are similar to those of centres with on site surgery.[3–6] In Belfast and in Edinburgh travel in an ambulance, which had resuscitation facilities, did not seem to cause any clinical deterioration.

In 1988 two sets of guidelines for carrying out coronary angioplasty were published.[7 8] Both strongly emphasised on site surgery but neither indicated the time limit for surgical back up. I suggest that we should consider a recommended time limit, perhaps of 120 minutes, between final occlusion and revascularisation. Such a limit, irrespective of whether the surgery is on site or off site, would help to maintain good standards in coordinating the scheduling of angioplasty cases with the surgical list and in limiting the time spent on attempts to reopen the occluded artery, and in the surgical unit getting the patient speedily through to reperfusion. More data on survival and myocardial preservation are needed to define an appropriate time limit more precisely. Although a small series reported by Reul *et al* suggested that infarction could be avoided when operation was performed within 25 minutes of the onset of ischaemia,[9] infarction rates of 27% and 44%[10] were found in large angioplasty centres where patients could be transferred directly to an operating theatre. O'Kane *et al* reported no deaths in 25 patients operated on at a mean of 285 minutes after occlusion.[11]

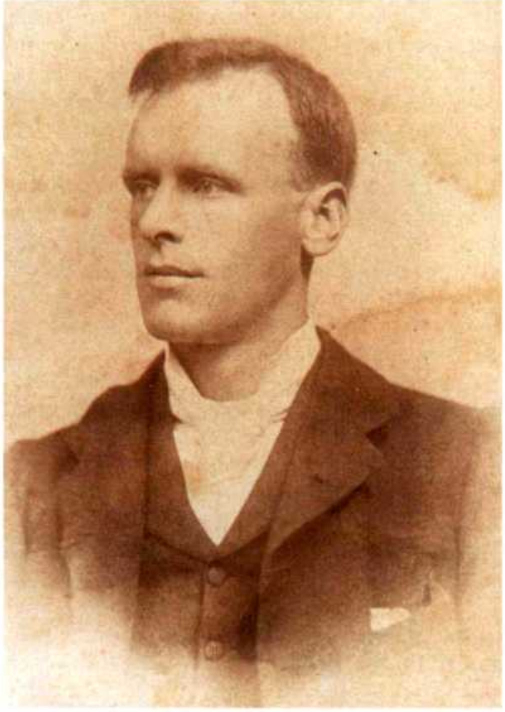
For most angioplasties the selection of cases is similar whether surgical back up is on site or off site. For both, the cardiologist and surgeon must judge that the patient has ventricular function and a coronary anatomy that will in the event of occlusion allow a viable circulation until cardiopulmonary bypass has been started. For very high risk angioplasty, in which occlusion might cause extensive myocardial impairment an aortic balloon pump or a femoral-femoral bypass support system is needed. The numbers of high risk patients treated by angioplasty are growing and such patients should only be treated with off site surgical back up if suitable transport with portable support systems is available and shown to be effective. This proviso also applies when the operating theatre is on site but remote from the cardiac laboratory. The need for surgical back up has been declining.[12] Although occlusion develops in 5% of patients treated by angioplasty our ability to reopen vessels has improved and only 3% need surgical back up while 97% do not. The use of stents, perfusion catheter/balloons, and other devices is likely to reduce the need further.

I believe therefore that it is reasonable for experienced cardiac laboratory teams to perform coronary angioplasty using nearby off site operating theatres if back up can be obtained within an appropriate time limit.

There are, however, difficult choices to be made about the plans for future facilities. There is much to be said in favour of combining invasive cardiology and cardiac surgery. Interventional cardiology will increase considerably and the choice of treatment will need closer medical and surgical discussion. Back up will be needed for various forms of non-surgical treatment. But should cardiology centralise or cardiac surgery decentralise? Should diagnostic angiography be separated from interventional cardiology? The management of recent onset and unstable angina may require much closer links between coronary care units and cardiac *x* ray suites but it is difficult to separate such admissions to coronary care units from general medical admissions and to send them direct to off site regional cardiac centres. Currently I think that coronary angioplasty with off site surgical back up makes the best use of the facilities we have.

1 Richardson SG, Morton P, Murtagh JG, O'Keefe DB, Murphy P, Scott ME. Management of acute coronary occlusion during percutaneous transluminal coronary angioplasty: experience of complications in a hospital without on site facilities for cardiac surgery. *Br Med J* 1990;**300**:355–8.
2 Shaw TRD, Starkey IR, Essop AR, *et al.* Emergency coronary bypass surgery after vessel occlusion at angioplasty in centres without on-site cardiac surgery [Abstract]. *Br Heart J* 1989;**61**:438.
3 Barner HB, Lea JW, Naunheim KS, Stoney WS. Emergency coronary bypass not associated with preoperative shock in failed angioplasty, after thrombolysis and for acute myocardial infarction. *Circulation* 1989; **79** (suppl I):152–9.
4 Golding LAR, Loop FD, Hollman JL, *et al.* Early results of emergency surgery after coronary angioplasty. *Circulation* 1986;**74**(suppl III):26–9.
5 Parsonnet V, Gielchinsy I, Hochberg MS, *et al.* Emergency surgery after failed angioplasty [Abstract]. *J Am Coll Cardiol* 1987;**9**:123A.
6 Talley JD, Weintraub WS, Anderson HV, *et al.* Late clinical outcome of coronary bypass surgery after failed angioplasty [Abstract]. *Circulation* 1987;**76** (suppl IV):352.
7 ACC/AHA Task Force Report. Guidelines for percutaneous transluminal coronary angioplasty. *J Am Coll Cardiol* 1988;**12**:529–45.
8 Bourassa MG, Alderman EL, Bertrand M, *et al.* Report of the Joint International Society and Federation of Cardiology/World Health Organisation Task Force on Coronary Angioplasty. *Eur Heart J* 1988;**9**:1034–45.
9 Reul GJ, Cooley DA, Hallman GL, *et al.* Coronary artery bypass for unsuccessful percutaneous transluminal coronary angioplasty. *J Thorac Cardiovasc Surg* 1984;**88**: 685–94.
10 Killen DA, Hamaker WR, Reed WA. Coronary artery bypass following percutaneous transluminal coronary angioplasty. *Ann Thorac Surg* 1985;**40**:133–8.
11 O'Kane H, Cleland J, Gladstone D, Galvin I, Buckels J. Emergency operation after failed percutaneous angioplasty: how late? *Br Heart J* 1989;**61**:93–4.
12 Detre K, Holubkov R, Kelsey S, *et al.* Percutaneous transluminal coronary angioplasty in 1985–1986 and 1977–1981: The National Heart, Lung and Blood Registry. *N Engl J Med* 1988;**318**:265–70.

VIEWS FROM THE PAST *Ernest Henry Starling*



To cardiologists, Starling is best known for his law of the heart, which indicated that cardiac output is determined by diastolic fibre length. Here we see him as a young man at the threshold of his career. In 1899, at the age of 33, he succeeded Sharpey-Schafer as Jodrell professor of physiology at University College, London (Lewis collection).

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Consult data sheet before prescribing.

Use: Hypertension when standard therapy is ineffective or inappropriate. Congestive heart failure (adjunctive therapy).

Presentation: Tablets containing 2.5mg, 5mg, 10mg or 20mg lisinopril ('Zestril').

Dosage and administration: Hypertension – initially 2.5mg daily, a 2.5mg dose seldom achieves a therapeutic response; adjust dose according to response. Maintenance usually 10-20mg once daily. Maximum is 40mg daily. Diuretic-treated patients – if possible stop diuretic 2-3 days before starting 'Zestril'. Resume diuretic later if desired.

Congestive heart failure (adjunctive therapy) – initially 2.5mg daily in hospital under close medical supervision, increasing to 5-20mg once daily according to response. Impaired renal function – may require a lower maintenance dose. 'Zestril' is dialysable. Elderly patients – no change from standard recommendations.

Contraindications: Pregnancy – stop therapy if suspected. Hypersensitivity to 'Zestril'. Patients reacting with angioneurotic oedema to previous ACE inhibitor treatment.

Precautions: Assessment of renal function is recommended. Renal insufficiency; renovascular hypertension; surgery/anaesthesia; possibility of hypotension especially in ischaemic heart disease and cerebrovascular disease. Combination with antihypertensives may increase hypotensive effect. Sometimes increased blood urea and creatinine and/or cases of renal insufficiency if given with diuretics. Minimises thiazide-induced hypokalaemia and hyperuricaemia. Potassium supplements potassium-sparing diuretics and potassium – containing salt substitutes not recommended. Indomethacin may reduce hypotensive effect. Possible reduced response ▼ Afro-Caribbean patients. Use with caution in breastfeeding mothers. Do not use in aortic stenosis or outflow tract obstruction or cor pulmonale. Monitor lithium serum levels if lithium salts administered.

Side effects: Dizziness, headache, diarrhoea, fatigue, cough and nausea. Less frequently, rash and asthenia. Rarely, angioneurotic oedema and other hypersensitivity reactions; renal failure; symptomatic hypotension (especially if volume-depleted); severe hypotension (more likely if severe heart failure); palpitation; hyperkalaemia; increases in liver enzymes and serum bilirubin (usually reversible on discontinuation of 'Zestril') and impotence.

Product licence numbers and basic NHS cost: 'Zestril' 2.5mg (29/0208) 28 tablets, £7.84. 5mg (29/0204) 28 tablets, £9.83, 10mg (29/0205) 28 tablets, £12.13, 20mg (29/0206) 28 tablets, £20.96.

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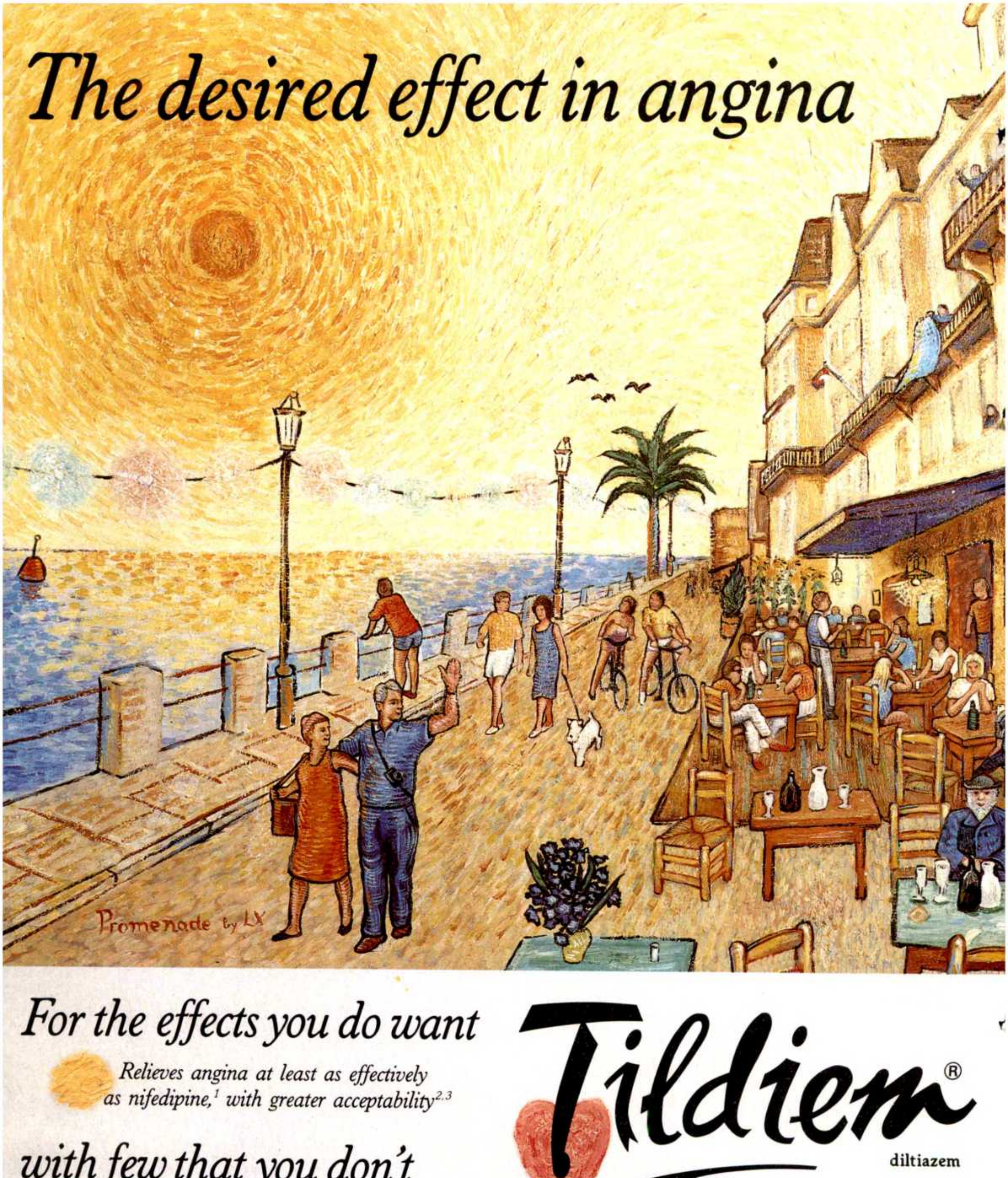
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Abbreviated Prescribing Information Presentation: Off-white, biconvex tablets each containing 60mg diltiazem hydrochloride in a modified release formulation. **Indication:** Angina pectoris. **Dosage:** General: Usual adult dose is one tablet (60mg) three times daily. Individual patient response may require up to 360mg daily in divided doses. A total daily dose of 480mg has been used with benefit, especially in patients with unstable angina. Elderly and patients with impaired hepatic or renal function: the recommended starting dose is one tablet (60mg) twice daily. Heart rate should be monitored; if below 50 beats per minute the dose should not be increased. **Contraindications:** Pregnancy and women of child bearing potential. Sick sinus syndrome, left ventricular failure with stasis, second or third degree AV block and severe bradycardia. **Warnings and precautions:** Caution in patients with reduced left ventricular function. Patients with mild bradycardia, first degree heart block or prolonged PR interval should be closely monitored for any worsening of these conditions. Caution should be observed in combination with drugs which may induce bradycardia or those with a hypotensive effect because of a possible additive effect. Plasma levels of digitalis glycosides, carbamazepine, cyclosporin and theophylline may be slightly raised in the presence of Tildiem. **Side effects:** Ankle oedema, malaise, headache, rash, hot flushes, gastrointestinal disturbances, rarely symptomatic bradycardia, sinoatrial block and atrioventricular block, vascular skin reactions, raised liver transaminases and isolated cases of hepatitis. **Pack size and basic NHS cost:** Blister strips of 10 tablets in packs of 100 tablets £15.00. **Product licence number:** PL4969/0005. Full prescribing information is available on request. Lorex and Tildiem are trade marks. **References** 1. Frishman WH et al, Am J Cardiol 1985; **56**: 41H-46H 2. Chaffman M, Brogden RN, Drugs 1985; **29**: 387-454 3. Schroeder JS Mod Medicine 1982; September: 94-116 4. Roberts R, Gibson R, J Cardiovasc Pharmacol 1989; **13** (Suppl. 1): S36-S46 5. MDPIT, New Eng J Med 1988; **319** no 7: 385-392.

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TI: J50a

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ORIGINAL ARTICLES

Intravenous streptokinase for acute myocardial infarction reduces the occurrence of ventricular late potentials

Eng-Wooi Chew, Patricia Morton, J Gerard Murtagh, Michael E Scott, D Barry O'Keeffe

Abstract

The occurrence of ventricular late potentials in survivors of acute myocardial infarction treated with intravenous streptokinase was compared with that in a conservatively treated group and the relation between ventricular late potentials and patency of the infarct related artery was examined. Of 115 patients admitted with a first infarct, 55 were treated with intravenous streptokinase (streptokinase group) and 60 were treated conservatively (non-streptokinase group). A signal averaged electrocardiogram was recorded in all patients and coronary angiography was performed in 45 (81·8%) of the streptokinase group and in 21 (35%) of the non-streptokinase group. At a 40 Hz filter setting ventricular late potentials were significantly less common in patients treated with streptokinase (9 (16·4%) of 55) than in those who were not (26 (43·3%) of 60). A total of 66 patients underwent angiography. Of the 26 who had closed infarct-related arteries, 17 had ventricular late potentials at a 40 Hz filter setting (sensitivity 65·4%, specificity 95%) and 38 of the 40 patients with a patent infarct-related artery did not have ventricular late potentials (sensitivity 80·9%, specificity 89·5%).

Patients with acute myocardial infarction treated with intravenous streptokinase were significantly less likely to have ventricular late potentials than conservatively treated patients and the absence of ventricular late potentials at 40 Hz filter setting was a good non-invasive predictor that the infarct-related artery was patent.

Over the past 10 years, several groups using special non-invasive processing techniques have detected low amplitude, high frequency potentials late in the QRS complex and in the ST segment on the surface electrocardiogram.[1-3] In experimental and clinical studies these correlated well temporally with fractionated electrograms recorded from damaged cardiac tissue.[4-6] Ventricular late potentials identify patients at risk of ventricular tachycardia after acute myocardial infarction and who are thus at increased risk of sudden cardiac death.[7-9]

Thrombolytic treatment reduces mortality after acute myocardial infarction[10-12] by limiting infarct size. Because thrombolysis also reduces the risk of ventricular arrhythmias we examined the proposition that ventricular late potentials were less common in patients with acute myocardial infarction who were treated with intravenous streptokinase than in those who were conservatively treated.

Some investigators have suggested that abrupt electrocardiographic repolarisation changes after thrombolytic treatment are predictive of (but with a low sensitivity (67%)) an open infarct-related artery.[13] The second object of our study, therefore, was to examine the relation between ventricular late potentials and patency of the infarct-related artery.

Patients and methods

PATIENTS

A total of 123 consecutive patients admitted to our cardiac unit with a first acute myocardial infarction were enrolled into the study. In all patients the diagnosis of acute myocardial infarction was confirmed clinically, electrocardiographically, and by serum concentrations of total creatine kinase (CK) and creatine kinase MB. Eight patients whose electrocardiogram showed bundle branch block were excluded from the study.

Of the remaining 115 patients, 55 satisfied our criteria for treatment with intravenous streptokinase (the thrombolytic agent used in our cardiac unit), which was given as an intravenous infusion of 1·5 million IU over 20 minutes within six hours of onset of chest pain (streptokinase group). These patients had clear electrocardiographic evidence of evolving myocardial infarction and no contraindication to thrombolytic treatment. All these patients were subsequently managed identically with oral aspirin and intravenous heparin for five days. The rest were treated conservatively (non-streptokinase group). Patients in this group were admitted after the six hour "limit" or had a contraindication to thrombolysis.

SIGNAL AVERAGING TECHNIQUE

A signal averaged electrocardiogram was recorded at the end of the first week after acute myocardial infarction on a commercial Marquette-15 (Marquette Electronics, Mil-

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waukee) machine that has a high resolution electrocardiogram option. The method is similar to that described by Simson[3] and Denes *et al.*[8] Other investigators have shown that the end of the first week is the best time to perform the recording.[7 9 14] They noted a steady increase in the occurrence of late potentials throughout the hospital stay and that once late potentials had appeared they tended to remain. Late potentials recorded within the first 24 hours may not reflect future risk because the anatomical and electrophysiological alterations of ischaemic myocardium in this phase are unstable.

We used bipolar orthogonal X, Y, Z leads; and signals from 500 beats were amplified, digitised, averaged, and then filtered with bidirectional high band pass filters at 25 Hz and 40 Hz. We chose to analyse the results at two filter frequencies because there is controversy about which is the best band pass filter frequency for recording ventricular late potentials. Previous work from Denes *et al*, Verzoni, *et al*, and Gomes *et al* suggests that the 40 Hz filter gives a better compromise between sensitivity and specificity.[8 15 16]

Signals from the three leads were combined into a vector magnitude $V=\sqrt{(x^2+y^2+z^2)}$. Automated measurements were provided for the duration of the composite electrogram—that is "filtered QRS duration" (normal $<$ 120 ms), the root-mean-square voltage of the last 40 ms of the filtered QRS complex (normal $>$ 20 μV), and the duration of the terminal low amplitude signals less than 40 μV (normal $<$ 38 ms). Ventricular late potentials were considered to be present if two or three of the above values were abnormal.

CORONARY ANGIOGRAPHY

Coronary angiography was performed in 45 (81·8%) of the streptokinase group and 21 (35%) of the non-streptokinase group. The decision to carry out coronary angiography was made by the attending cardiologist who was unaware of the results of the signal-averaged electrocardiogram. Often they were patients who had angina or inducible ischaemia on treadmill testing after infarction. The infarct-related artery was identified on the basis of electrocardiographic abnormalities in the acute phase. The degree of residual stenosis was graded according to the criteria of the TIMI (thrombolysis in myocardial infarction) trial investigators.[17] Vessels in TIMI grades 2 or 3 were classified as "open".

STATISTICAL ANALYSIS

We used the χ^2 test with Yates's correction for dichotomous variables and the two sample *t* test for continuous variables. We performed regression analysis using the presence or absence of ventricular late potentials as the dependent variable and the characteristics listed in the table as the independent variables. The level of statistical significance was set at 0·05 or 1 in 20.

Results

Figure 1 shows the signal averaged electrocardiogram of a patient treated with intravenous streptokinase and fig 2 shows the signal averaged electrocardiogram of a patient treated by conventional means. The table shows the characteristics of patients in the two groups.

When analysed singly, three variables seemed to influence the presence of late potentials. These were the administration of streptokinase, patency of the infarct-related artery, and age. As the table shows, patients treated with intravenous streptokinase for acute myocardial infarction were less likely to have ventricular late potentials at the 40 Hz filter setting (9 of 55 (16·4%) in the streptokinase group compared with 26 of 60 (43·3%) in the

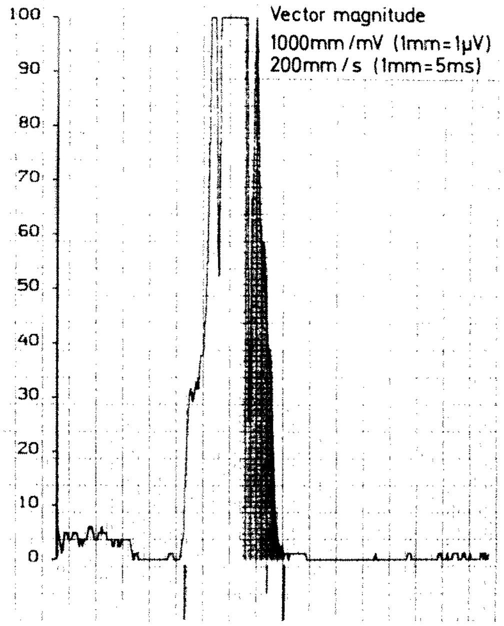


Figure 1 Signal averaged electrocardiogram from a patient with acute myocardial infarction treated with intravenous streptokinase. Shaded area represents last 40 ms of filtered QRS complex. Filtered QRS duration = 92 ms (normal); root-mean-square voltage of last 40 ms = 90 μV (normal); duration of terminal signals less than 40 μV = 16 ms (normal).

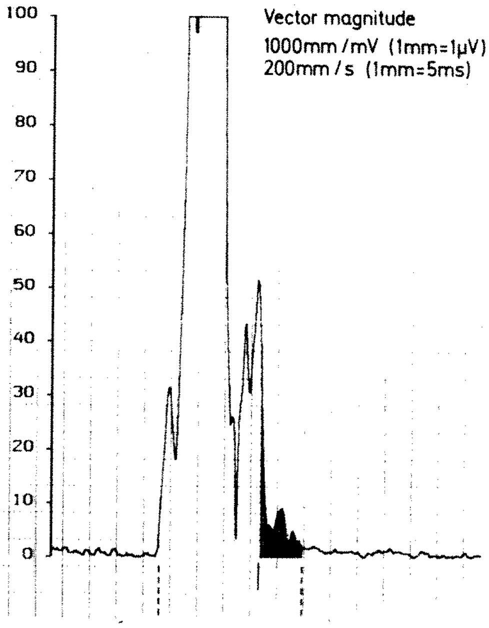


Figure 2 Signal averaged electrocardiogram from a patient with acute myocardial infarction treated conservatively. Shaded area represents last 40 ms of filtered QRS complex. Filtered QRS duration = 132 ms (abnormal); root-mean-square voltage of last 40 ms = 13 μV (abnormal); duration of terminal signals less than 40 μV = 40 ms (abnormal).

Characteristics (mean (SD)) of patients in streptokinase and non-streptokinase groups

Variable		*Streptokinase (n = 55)*	*Non-streptokinase (n = 60)*	*p value*
Age (mean (SD))		56·8 (12·4)	61·6 (10·5)	0·048
Number of men (%)		46 (84%)	41 (68%)	NS
Peak CK (U/l) (mean (SD))		1301 (1049)	1335 (806)	NS
Site of MI				
Anterior		30 (54·5%)	39 (65%)	NS
Inferior		22 (40%)	18 (30%)	NS
Others		3 (5·5%)	3 (5%)	NS
Number with VLP at:	40 Hz	9 (16·4%)	26 (43·3%)	0·003
	25 Hz	2 (3·6%)	6 (10%)	NS
Patent artery (%)		32 of 45 (71%)	8 of 21 (38%)	NS

CK, creatine kinase, MI, myocardial infarction; VLP, ventricular late potentials.

non-streptokinase group (p = 0·003)). The patency of the infarct-related artery also significantly influenced the presence of ventricular late potentials. Of the 26 patients with a closed infarct-related artery, 17 (65·4%) had late potentials compared with two (5%) of 40 patients with a patent infarct-related artery (p < 0·0001). Patients with ventricular late potentials also tended to be older (p = 0·048). The occurrence of ventricular late potentials did not seem to be influenced by the other variables such as sex, peak creatine kinase, and infarct site.

The occurrence of ventricular late potentials at 25 Hz in the two groups was not significantly different (although there was a trend towards a lower incidence in the streptokinase group—two (3·6%) of 55 in the streptokinase group compared with six (10%) of 60 in the non-streptokinase group (p = 0·33). At 25 Hz the patency of the infarct-related artery was not significantly associated with the occurrence of ventricular late potentials—three (11·5%) of 26 occluded arteries and two (5%) of 40 open arteries had late potentials (p = 0·57).

Of 66 patients who underwent angiography, 26 had closed infarct-related arteries. Of these, 17 had ventricular late potentials at 40 Hz (sensitivity 65·4%, specificity 95%) but only three had ventricular late potentials at 25 Hz (sensitivity 11·5%, specificity 95%). In 38 of the 40 patients with a patent infarct-related artery, there were no ventricular late potentials at a 40 Hz filter setting (sensitivity 80·9%, specificity 89·5%). At 25 Hz the corresponding sensitivity was 62·3% and the specificity was 60%.

When we used multifactorial analysis to examine the relation between the presence of late potentials and the other variables, the best predictor was the patency of the infarct-related artery followed by the administration of intravenous streptokinase and an inferior site of the infarct. The effect of the patency of the infarct-related artery was independent of that of streptokinase. The influence of age, apparent initially, became unimportant when these variables were taken into account.

Discussion

Most clinical studies of ventricular late potentials have examined their ability to identify patients at risk of ventricular arrhythmias after acute myocardial infarction. We showed that ventricular late potentials were less common in patients with acute myocardial infarction treated with intravenous streptokinase than in those treated conservatively. Our study also showed that the absence of ventricular late potentials after acute myocardial infarction is a good, non-invasive predictor of the patency of the infarct-related artery. This may be valuable information because thrombolytic treatment is now widely used and the absence of ventricular late potentials may help to identify those patients who will benefit most from coronary arteriography and perhaps further invasive treatment.

Our study showed that the patency of the infarct-related artery exerts an independent effect on the presence of late potentials. Our data, in accord with those of others,[9,18,19] do not suggest that the presence or absence of ventricular late potentials correlate with left ventricular ejection fraction. Successful thrombolytic treatment results in an electrically more stable myocardium[20-22] and Braunwald has suggested that a patent, blood-filled, infarct-related artery and vascular bed may provide a scaffolding that limits expansion of the necrotic myocardium.[23] We further propose that the lower incidence of ventricular late potentials in patients treated with intravenous streptokinase may be related to the reduction in mortality in this group compared with a conservatively treated group.

Gang *et al* found that the occurrence of ventricular late potentials in acute myocardial infarction was significantly less after successful thrombolytic treatment with tissue plasminogen activator (5%) than after conservative treatment (23%).[19] Of the 157 patients studied by Eldar *et al*, 65 were treated with thrombolysis (24 with streptokinase and 41 with tissue plasminogen activator).[24] The frequency of late potentials in this group was 14%, compared with 22·5% in a conservatively treated group. Our results accord with these findings but we found that a higher percentage of patients in both groups (16·4% and 43·3% respectively) had ventricular late potentials. This may be explained by the different filter frequencies used and different definition of ventricular late potentials. The thrombolytic agent administered may be relevant because initial reports from the TIMI trial (phase 1) suggest that tissue plasminogen activator results in higher patency rates of the infarct-related artery than streptokinase.[17] Our figure of 43·3% for late potentials in the conservatively treated group of patients is similar to that found by other investigators.[25,26]

The problems remain of standardising the technique of surface signal averaging and of defining ventricular late potentials in order to compare results between centres. In most studies, the choice of filter setting has been arbitrary. Gomes *et al* showed that a 25 Hz filter setting gave a low sensitivity but the best specificity, whereas a 80 Hz filter provided best sensitivity but low specificity.[16] A 40 Hz filter provides a sensitivity and a specificity intermediate between those at 25 Hz and 80 Hz. Furthermore, Denes *et al* showed that the 40 Hz filter gives better reproducibility of measurements.[8] For these reasons we used the 40 Hz filter in our analysis. Ventricular late potentials detected at 40 Hz filter setting were a more sensitive and specific method of predicting the patency of the infarct-related artery than the results at 25 Hz. We think that the 25 Hz filter underestimates the occurrence of ventricular late potentials. Gang *et al* used the 25 Hz filter in their study and found that patients with closed infarct-related arteries had a higher (but not statistically significant) incidence of ventricular late potentials than those with open arteries.[19] Our study showed that the 40 Hz filter was better in predicting patency of the infarct-related artery. We are awaiting the results of a long term follow up in these patients, to compare the results with the 25 Hz filter with those with the 40 Hz filter. Preliminary results suggest that the 40 Hz filter may give the result that best predicts long term clinical outcome.

Our results showed a relation between late potentials and inferior infarcts. This was also noted by Kuchar *et al*[7] but not by McGuire *et al*[14] or Gang *et al.*[19] The reason for this discrepancy may be related to the size of the study population and different definitions of late potentials used. It may be that because the inferior wall of the heart is one of the later parts to depolarise, low amplitude signals that originate there are more likely to become apparent.[27]

This was not a randomised, placebo controlled study because early reperfusion is known to improve survival after acute myocardial infarction and we thought that a randomised trial would be unethical. Patients in the conventionally treated group presented after the six hour "limit" or had contraindications to treatment with streptokinase. Apart from this difference they are a group (table) that is comparable in age, sex, and site of infarct with the streptokinase group.

From this study, we conclude that intravenous streptokinase administered for acute myocardial infarction and the presence of an open infarct-related artery exert independent effects on the presence of late potentials. The absence of ventricular late potentials after acute myocardial infarction seems to be a good non-invasive predictor of the patency of the infarct-related artery. Detection of ventricular late potentials after thrombolytic treatment therefore is an additional non-invasive, simple means of predicting patency of the infarct-related artery and may help in selecting which patients require detailed invasive investigations.

We thank Dr G McKenzie for his advice on the statistical analysis of the results

1 Uther JB, Dennett CJ, Tan A The detection of delayed activation signals of low amplitude in the vectorcardiograph of patients with recurrent ventricular tachycardia by signal averaging. In Sandoe E, Julian DG, Bell JW, eds *Management of ventricular tachycardia-role of mexilitine.* Amsterdam: Excerpta Medica, 1978.80.

2 Berbari EJ, Scherlag BJ, Hope RR, Lazzara R Recording from the body surface of arrhythmogenic ventricular activity during the ST-segment. *Am J Cardiol* 1978; 41·697–702

3 Simson MB Use of signals in the terminal QRS complex to identify patients with ventricular tachycardia after myocardial infarction *Circulation* 1981;64 235–42.

4 Simson MB, Untereker WJ, Spielman SR, *et al* Relation between late potentials on the body surface and directly recorded fragmented electrograms in patients with ventricular tachycardia *Am J Cardiol* 1983,57:105–12

5 Gardner PI, Ursell PC, Fenoglio JJ Jr, Wit AL. Electrophysiologic and anatomic basis for fractionated electrograms recorded from healed myocardial infarct. *Circulation* 1985;72·596–611.

6 Boineau JP, Cox JL Slow ventricular activation in acute myocardial infarction. a source of re-entrant premature ventricular contraction *Circulation* 1973;48:702–13.

7 Kuchar DL, Thorburn CW, Sammel NL. Late potentials detected after myocardial infarction· natural history and prognostic significance. *Circulation* 1986;74:1280–9.

8 Denes P, Santarelli P, Hauser RG, Uretz EF Quantitative analysis of the high-frequency components of the terminal portion of the body surface QRS in normal subjects and in patients with ventricular tachycardia. *Circulation* 1983, 67:1129–38

9 Verzoni A, Romano J, Pozzoni L, Tarricone D, Sangiorgio S, Croce L Prognostic significance and evolution of late ventricular potentials in the first year after myocardial infarction: a prospective study. *PACE* 1989;12:41–51

10 Gruppo Italiano per lo Studio della Streptochinasi nell' Infarto Miocardico (GISSI). Effectiveness of intravenous thrombolytic treatment in acute myocardial infarction *Lancet* 1986;i:397–402.

11 Yusuf S, Collins R, Peto R Intravenous and intracoronary fibrinolytic therapy in acute myocardial infarction· overview on results on mortality, reinfarction and side-effects from 33 randomized, controlled trials *Eur Heart J* 1985;6.556–85.

12 Simoons ML, Serruys PW, van den Brand M, *et al.* Improved survival after early thrombolysis in acute myocardial infarction: a randomised trial by the Interuniversity Cardiology Institute in The Netherlands. *Lancet* 1985,ii.578–82.

13 Richardson SG, Morton P, Murtagh JG, Scott ME, O'Keeffe DB. Relation of coronary arterial patency and left ventricular function to electrocardiographic changes after streptokinase treatment during acute myocardial infarction. *Am J Cardiol* 1988;61:961–5

14 McGuire M, Kuchar D, Ganis J, Sammel M, Thorburn C. Natural history of late potentials in the first ten days after acute myocardial infarction and relation to early ventricular arrhythmias *Am J Cardiol* 1988;61·1187–90.

15 Verzoni A, Romano S, Tarricone D, Sangiorgio S, Croce L. Quantitative analysis of the high-frequency components of the signal-averaged QRS complex in normal subjects and in patients with ventricular tachycardia. *New Trends in Arrhythmias* 1987,3:7–16.

16 Gomes JA, Winters SL, Stewart D, Targonski A, Barreca P. Optimal band pass filters for time domain analysis of the signal-averaged electrocardiogram. *Am J Cardiol* 1987,60·1290–8.

17 Chesebro JH, Knatterud G, Roberts R, *et al.* Thrombolysis in Myocardial Infarction (TIMI) trial, phase 1: a comparison between intravenous tissue plasminogen activator and intravenous streptokinase Clinical findings through hospital discharge. *Circulation* 1987,76·142–54.

18 Pollak SJ, Kertes PJ, Bredlau CE, Walter PF. Influence of left ventricular function on signal averaged late potentials in patients with coronary artery disease with and without ventricular tachycardia. *Am Heart J* 1985;110 747–52.

19 Gang ES, Lew AS, Hong MA, Wang FZ, Siebert CA, Peter T Decreased incidence of ventricular late potentials after successful thrombolytic therapy for acute myocardial infarction. *N Engl J Med* 1989;321:712–6.

20 Vermeer F, Simoons ML, Lubsen J Reduced frequency of ventricular fibrillation after early thrombolysis in myocardial infarction. *Lancet* 1986;i:1147–8.

21 Kersschot IE, Brugada P, Ramentol M, *et al.* Effects of early reperfusion in acute myocardial infarction on arrhythmias induced by programmed stimulation· a prospective, randomised study *J Am Coll Cardiol* 1986;7:1234–42.

22 Sager P, Perlmutter R, Rosenfeld L, McPherson C, Wackers F, Batsford W Thrombolysis decreases sudden death and arrhythmogenic potential after anterior myocardial infarction with aneurysm formation [Abstract]. *Circulation* 1987;76(suppl IV):IV–261

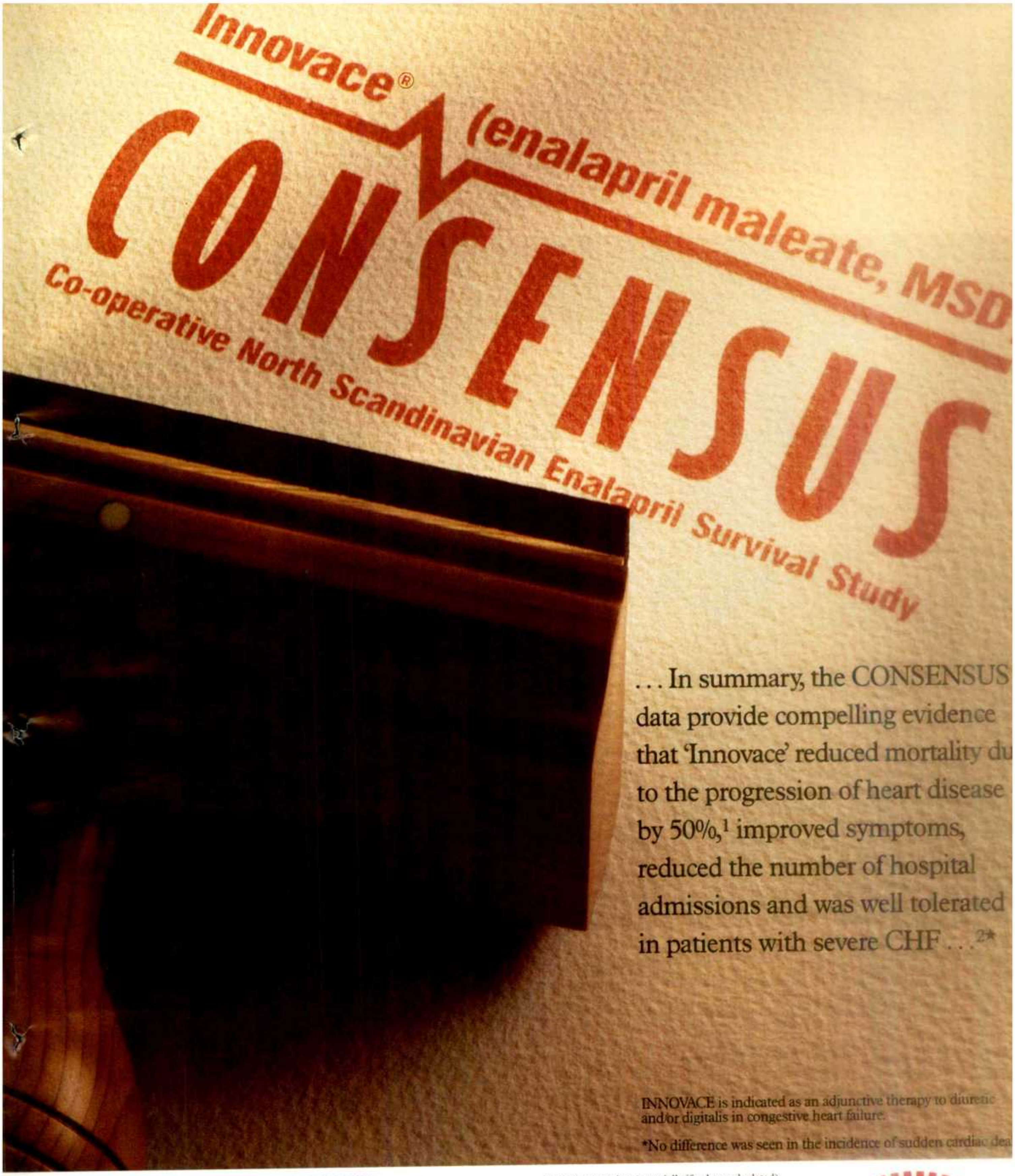
23 Braunwald E. Myocardial reperfusion, limitation of infarct size, reduction of left ventricular dysfunction, and improved survival Should the paradigm be expanded? *Circulation* 1989,79 441–4.

24 Eldar M, Leor J, Hod H, Rotstein Z, Truman S, Kaplinsky E, Abboud S. Effect of thrombolysis on the evolution of late potentials within 10 days of infarction *Br Heart J* 1990;63 273–6

25 Gomes JA, Mehra R, Barreca P, El-Sherif N, Hariman R, Holtzman R. Quantitative analysis of the high frequency components of the signal-averaged QRS complex in patients with acute myocardial infarction a prospective study. *Circulation* 1985,72·105–11.

26 Breithardt G, Schwarmaier J, Borggrefe M, *et al.* Prognostic significance of late ventricular potentials after acute myocardial infarction. *Eur Heart J* 1983;4:487–95.

27 Breithardt G, Borggrefe M. Pathophysiological mechanisms and clinical significance of ventricular late potentials. *Eur Heart J* 1986;7.364–85.



… In summary, the CONSENSUS data provide compelling evidence that 'Innovace' reduced mortality du to the progression of heart disease by 50%,[1] improved symptoms, reduced the number of hospital admissions and was well tolerated in patients with severe CHF …[2*]

INNOVACE is indicated as an adjunctive therapy to diuretic and/or digitalis in congestive heart failure.

*No difference was seen in the incidence of sudden cardiac dea

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Refer to Data Sheet before prescribing.

INDICATIONS

Hypertension where standard therapy is ineffective or inappropriate. Congestive heart failure (adjunctive therapy).

DOSAGE AND ADMINISTRATION

Hypertension: Initially 5 mg once daily, reduce starting dose to 2.5 mg if over 65 years, on diuretics or renally impaired. Adjust dose according to response; maintenance usually 10-20 mg once daily. Maximum dose 40 mg daily. Diuretic-treated patients – if possible stop diuretic two to three days before starting 'Innovace'. Resume diuretic later if required.

Congestive heart failure (adjunctive therapy): Initially, 2.5 mg daily in hospital under medical supervision, increasing to the usual maintenance dose of 10-20 mg once daily according to response.

Impaired renal function: May require a lower maintenance dose. 'Innovace' is dialysable.

CONTRA-INDICATIONS

Pregnancy – stop therapy if suspected. Hypersensitivity to 'Innovace'. Patients reacting with angioneurotic oedema to previous ACE-inhibitor treatment.

PRECAUTIONS

Assess renal function prior to therapy with 'Innovace' and during therapy where appropriate.

Renal insufficiency; renovascular hypertension; possibility of hypotension especially in ischaemic heart disease or cerebrovascular disease; surgery/anaesthesia.

Combination with antihypertensives may increase hypotensive effect. Sometimes increased blood urea and creatinine and/or cases of renal insufficiency if given with diuretics. Minimises thiazide-induced hypokalaemia and hyperuricaemia. Potassium supplements, potassium-sparing diuretics, and potassium-containing salt substitutes are not recommended. Possible reduced response in Afro-Caribbean patients. Use with caution in breast-feeding mothers. Do not use in aortic stenosis, or outflow tract obstruction. Monitor serum levels of lithium, if lithium salts are given.

SIDE EFFECTS

Dizziness, headache. Others include fatigue, asthenia, nausea, diarrhoea, muscle cramps, rash, dysgeusia, cough.

Less commonly, angioneurotic oedema; other hypersensitivity reactions; renal failure; symptomatic hypotension (especially if volume-depleted); severe hypotension (more likely if severe heart failure); hyperkalaemia; hypokalaemia; increases in liver enzymes and serum bilirubin (usually reversible on discontinuation of 'Innovace'); paraesthesiae; impotence.

BASIC NHS COST

2.5 mg tablets, £10.00 for bottles of 50.
5 mg tablets, £7.86 for 28-day calendar pack.
10 mg tablets, £11.03 for 28-day calendar pack.
20 mg tablets, £13.10 for 28-day calendar pack.

Product licence numbers:

2.5 mg tablets, 0025/0220; 5 mg tablets, 0025/0194; 10 mg tablets, 0025/0195; 20 mg tablets, 0025/0196.

Issued December 1989.

▼ Special reporting to the CSM required.
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References

1. CONSENSUS Trial Study Group, *New Engl. J. Med.*, 1987, **316**, 1429.
2. Kjekshus, J., and Swedberg, K., *Amer. J. Cardiol.*, 1988, **62**, 67A-72A.

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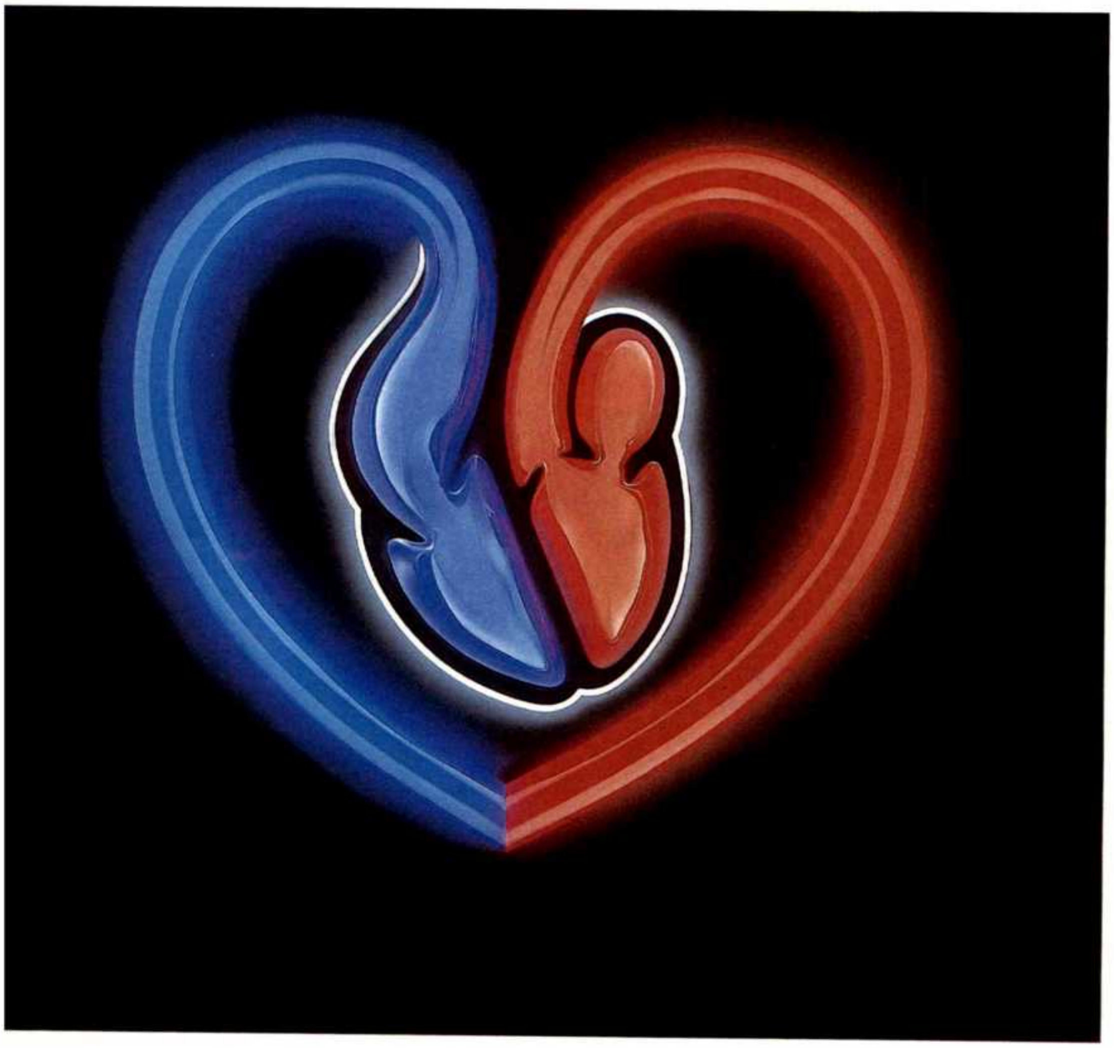

- Dual action improves myocardial contractility whilst reducing preload and afterload[1,2]
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Presentation: **Perfan Injection ▼** is a 5mg/ml solution of enoximone presented in ampoules containing 20ml. Perfan Injection is a sterile, clear yellow solution (pH approximately 12.0) for intravenous administration which must be diluted before use. Containers of diluted product are intended for single use only. **Uses:** *Actions:* Perfan has positive inotropic and vasodilator properties. *Indications:* Perfan Injection is indicated for the treatment of congestive heart failure, typically where cardiac output is reduced and filling pressures increased, in patients who require intravenous therapy and who can be closely monitored. **Dosage and Administration:** Perfan Injection must be diluted before use. Dilutions should be used immediately and any unused portion discarded. *Dilution:* The pH of Perfan Injection is approximately 12.0. Perfan Injection must be diluted with an equal volume of 0.9% Sodium Chloride Injection or Water for Injections before administration. 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Perfan Injection should be used during pregnancy only if the potential benefit justifies the potential risk. It is not known whether this drug is excreted in human milk. Caution should be exercised when Perfan Injection is administered to a nursing mother. *Precautions:* Perfan Injection should be used cautiously when heart failure is associated with hypertrophic cardiomyopathy, stenotic or obstructive valvular disease or other outlet obstruction. During treatment with Perfan Injection the following parameters should be monitored: blood pressure, heart rate, ECG, central venous pressure and fluid and electrolyte status. Monitoring of platelet counts and hepatic enzyme levels is recommended. *Side Effects:* Whilst Perfan has not been shown to be arrhythmogenic in electrophysiological studies, ectopic beats have been observed in some patients during or after Perfan administration. 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Other drugs should not be mixed in the same container as Perfan Injection. **Legal category:** POM. **Package quantities:** Ampoules of 20ml in cartons of 10 ampoules. **Product licence no:** PL 4425/0086. **Name and Address of Licence Holder:** Merrell Dow Pharmaceuticals Ltd., Lakeside House, Stockley Park, Uxbridge, Middlesex UB11 1BE. **NHS Cost:** Carton of 10 ampoules £154.00. See full prescribing information before administering this product. **Date of last review:** January 1990. **References:** 1. Herrman HC et al. Circulation 1987; **75** 1214-1221. 2. Crawford MH Am. J. Cardiol. 1987; **60** 42C-45C. 3. Amin DK et al. Am. Heart J. 1984; **108** 1285-1292. Further information is available on request.

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Raised plasma concentrations of atrial natriuretic peptide are independent of left atrial dimensions in patients with chronic atrial fibrillation

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Abstract

The aim of the present study was to determine whether left atrial size—a likely indicator of atrial stretching—correlates with the plasma concentration of atrial natriuretic peptide and whether this relation is different in patients in sinus rhythm and in those with atrial fibrillation. Arterial plasma concentrations of immunoreactive atrial natriuretic peptide (ir-ANP), adrenaline, noradrenaline, aldosterone, and vasopressin were measured in 13 patients in sinus rhythm without apparent heart failure and in 13 patients in atrial fibrillation. The two groups were matched for left atrial diameter and the ratio of the left atrial diameter to the diameter of the aortic root (assessed by echocardiography). There were no significant differences in age, heart rate, blood pressure, or left ventricular end diastolic diameter between the two groups. Left atrial diameters varied from 33 to 60 mm. The mean (SD) plasma concentration of ir-ANP was significantly higher (35 (21) pmol/l) in the patients with atrial fibrillation than in those in sinus rhythm (12 (11) pmol/l). The concentration of plasma aldosterone was also higher in patients with atrial fibrillation (831 (366) *v* 523 (211) pmol/l). Concentrations of adrenaline, noradrenaline, and vasopressin were similar in both groups. None of the hormone concentrations correlated with left atrial dimensions.

These results indicate that plasma concentrations of ir-ANP and aldosterone are highly sensitive indicators of changes in haemodynamic function during atrial fibrillation. They also underscore the difficulties of correlating echocardiographic assessment of patients with plasma concentrations of a vasoactive hormone.

The discovery of the atrial natriuretic peptide (ANP)—a hormonal link between the heart and the kidney—evoked new interest in the mechanisms of heart-kidney interactions.[1] Atrial stretch is held to be the major stimulus for release of ANP.[2] This peptide has potent natriuretic, vaso-relaxant, and aldosterone-inhibiting properties.[3–5] Plasma concentrations of immunoreactive (ir)-ANP increased during paroxysmal atrial fibrillation and decreased after successful electric cardioversion.[6–8] The left atrial diameter was reported to increase with the duration of atrial fibrillation.[9] This increase might be attributable to long-standing stretching of the left atrial wall caused by a continuously raised atrial pressure leading to dilatation. The aim of the present study was to determine whether left atrial size—a likely indicator of such stretching—corresponds to the plasma concentration of ANP and whether this relation is different in patients in sinus rhythm and in those with atrial fibrillation.

Patients and methods

PATIENTS

The study group was selected from 52 patients admitted during 1982 and 1983 to our cardiac department with atrial fibrillation of short duration. All patients were successfully cardioverted and were subsequently followed up in the outpatient clinic. Thirteen patients with a mean (SD) age of 63 (7) years were still in sinus rhythm in 1988. From the group of patients who had relapsed into atrial fibrillation we selected 13 patients to form matching pairs with the 13 patients still in sinus rhythm (table 1). All were in New York Heart Association functional class I. Two patients in each group had an old myocardial infarction and four patients in the atrial fibrillation group and two patients in sinus rhythm had type II diabetes mellitus. Radiological signs of decompensation—that is redistribution of blood in the lung, widened or poorly outlined pulmonary vessels, Kerley B lines, or interstitial oedema—were not found on chest *x* ray.[10] Table 1 gives the relative heart volume.[11] All patients were maintained on their regular medication, including digoxin, diuretics, β blockers, calcium antagonists, and class I antiarrhythmic agents. The drug intake was similar in the two groups except that seven of the patients in sinus rhythm and two in atrial fibrillation were taking class I antiarrhythmic agents. Only

Table 1 Patient characteristics (mean (SD))

Variable	*Sinus rhythm*	*Atrial fibrillation*
No	13	13
Age (years)	63 (7)	64 (5)
LAD/AO ratio	1·24 (0·14)	1·24 (0·16)
LAD (mm)	44 (6)	45 (6)
LVEDD (mm)	54 (10)	49 (6)
HR (beats/min)	64 (12)	66 (14)
BPs (mm Hg)	148 (14)	147 (17)
BPd (mm Hg)	86 (9)	88 (7)
Heart volume (ml/m^2)*	525 (79)	551 (125)

No statistically significant differences were found (paired *t* test)
LAD, left atrial diameter, AO, aortic root diameter, LVEDD, left ventricular end diastolic diameter, HR, heart rate, BPs, systolic blood pressure, BPd, diastolic blood pressure
* Assessed by chest *x* ray.[11]

patients in the atrial fibrillation group (n = 4) were taking calcium antagonists. Informed consent was obtained from each patient and the study was approved by the local ethics committee.

PROTOCOL

We used an Interspec Cardioscan echocardiograph. The heart was visualised from the left sternal border with the patient in the left lateral position. All examinations were undertaken by the same echocardiographer. The leading edge method was used for measurements.[12,13] A left ventricular end diastolic dimension, left atrial end systolic dimension, and a diastolic aortic root dimension were measured in millimetres in a long axis view obtained from the left sternal border.

Immediately after the echocardiographic investigation and with the patient remaining in the supine position, an arterial blood sample was drawn to measure the concentrations of ir-ANP, vasopressin, aldosterone, adrenaline and noradrenaline in plasma. These samples were taken after 45–60 minutes of rest.

RADIOIMMUNOASSAY

Blood samples were drawn into chilled heparinised tubes and centrifuged within 10 minutes. Plasma samples were stored at −20°C until they were processed. ANP was measured by a competitive radioimmunoassay based on antiserum RAS 8798 (Peninsula, CA, USA) raised in a rabbit against alpha human ANP. The radioligand, ^{125}I ANP, was purchased from Amersham (England) and the standard was synthetic human ANP (Peninsula). The IC$_{50}$ value concentration of unlabelled peptide in the assay tube inhibiting the maximal binding by 50% of the antiserum was 8·9 pmol/l. The antiserum cross reacts 100% with ANP (8–33), 60% with ANP (8–28), and 10% with auriculin A, but does not cross react with oxytocin or Arg 8 vasopressin. Plasma samples of 1·0 ml were extracted with Sep Pak (Waters, USA) as described by Theodorsson-Norheim *et al.*[14] The recovery of synthetic human ANP added to human plasma was 83% at 25 pmol/l and 85% at 100 pmol/l (n = 5 in each group). The standards and samples were incubated with the antiserum at 4°C and the radioligand was then added; this was followed by a further 24 hour incubation. Bound radioligand was separated from free radioligand by a donkey–antirabbit IgG solid face second antibody coated cellulose suspension (Sac-Cel, Wellcome). The interassay coefficient of variation was 11%. In 23 healthy individuals (mean age 63 (4) years) the mean plasma concentration of ir-ANP was 18 (9) pmol/l.

Plasma concentrations of arginine vasopressin were measured by a commercial radioimmunoassay (Bühlman, Basel).[15] The normal reference value for the plasma concentration of immunoreactive arginine vasopressin (AVP) at rest was <5·5 pmol/l.[16] Aldosterone was analysed by a commercial radioimmunoassay (CIS, Biomedica, Saluggia, Italy) and the normal reference value was <860 pmol/l.[17,18] Adrenaline and noradrenaline were measured by high performance liquid chromatography with electrochemical detection.[19,20] The reference value for adrenaline was <0·48 nmol/l and for noradrenaline it was <2 3 nmol/l.

STATISTICAL ANALYSIS

Values are expressed as mean and standard deviation. Linear regression analysis and Pearson's correlation coefficient were used to estimate the relation between the left atrial dimensions and the plasma concentrations of the hormones. Differences between the two patient groups were tested with the paired *t* test. p values of < 0·05 were regarded as significant.

Results

Table 2 shows the results of the hormone analysis. The left atrial dimensions and the ratio of the left atrial diameter to the diameter of the aortic root varied considerably (33–60 mm and 1·03–1·48 respectively). No significant differences in heart rate, blood pressure, left ventricular end diastolic dimension, or concentrations of adrenaline and noradrenaline were found between the groups. The mean plasma concentration of ir-ANP was significantly higher in the group with atrial fibrillation than in the sinus rhythm group (35 (21) and 12 (11) pmol/l respectively; p = 0·003) (fig 1A). The mean plasma concentration of aldosterone (fig 1B) was also higher in patients with atrial fibrillation than in the group in sinus rhythm (831 (336) *v* 523 (211) pmol/l; p = 0·003). The mean noradrenaline, adrenaline, and vasopressin concentrations were all close to the upper normal limit but no statistically significant differences were found between the two groups. Figure 2 shows the relations between the left atrial dimensions and the measured hormones. We found no correlation in either group between left atrial diameter or left atrial diameter/aortic root diameter ratio and the plasma concentration of any of the hormones that we measured (table 3).

Discussion

Awareness that the heart secretes a peptide with natriuretic, vasodilating, and aldosterone-inhibiting properties has revitalised interest in the physiological and pathophysiological link between the atria and the control of fluid and electrolyte balance. Concentrations of this peptide were increased in conditions associated with raised atrial filling pressures.[21] Furthermore, paroxysmal atrial fibrillation has been shown to increase plasma concentrations of ANP, and successful treatment with electrical

Table 2 Hormone concentrations (mean (1 SD))

	Sinus rhythm	*Atrial fibrillation*	*p Value*
ir-ANP (pmol/l)	12 (11)	35 (21)	0·003
Aldosterone (pmol/l)	523 (211)	831 (366)	0 003
Adrenaline (nmol/l)	0 31 (0 14)	0 44 (0·31)	NS
Noradrenaline (nmol/l)	2 33 (0·9)	2 34 (0 76)	NS
Arginine vasopressin (pmol/l)	6 5 (7 2)	5 4 (3 9)	NS

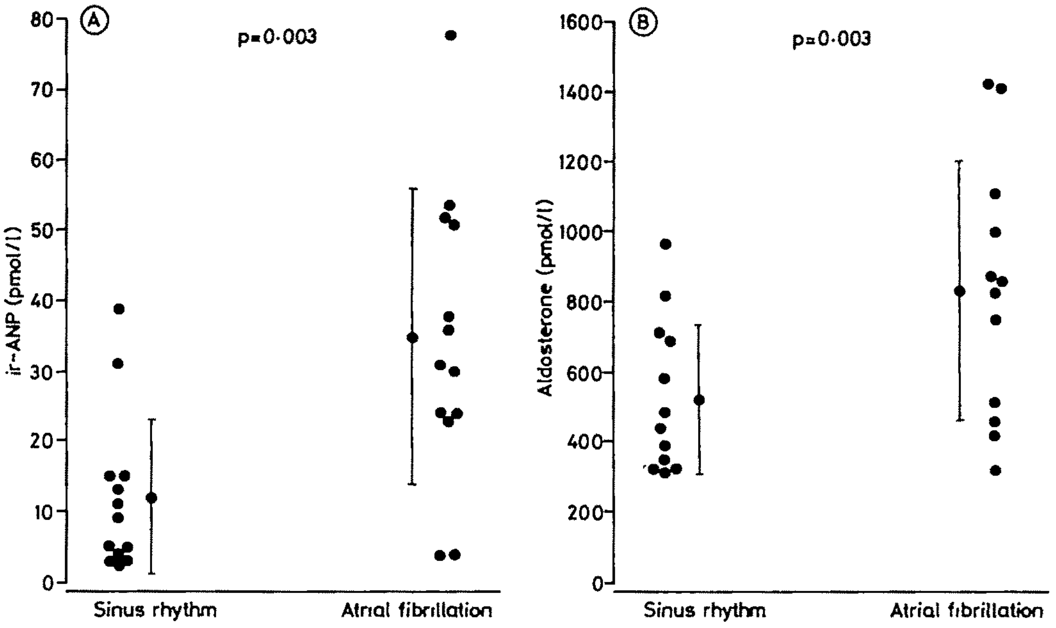

Figure 1 (A) Plasma concentrations of ir-ANP (mean (1 SD)) in 13 patients in sinus rhythm and in 13 with atrial fibrillation. (B) Plasma aldosterone concentrations (mean (1 SD)) in 12 patients in sinus rhythm and in 12 with atrial fibrillation.

cardioversion is followed by a decrease in plasma ANP.[7,8] Whether these findings are fully explained by haemodynamic alterations in the atrium during atrial fibrillation or whether the reduced frequency of the atrial contractions in itself is an important factor is at present unknown; though it has been suggested that raised atrial pressure during atrial fibrillation may be the main cause of the increased concentration of ANP.[22] An increase in left atrial dimensions with the duration of atrial fibrillation was reported, a finding that may be interpreted as a result of long-standing unfavourable distension of the left atrium.[9] If we assume that ANP release is mediated by atrial stretch, it is not unreasonable to expect some correlation with atrial diameters, especially in patients with chronic atrial fibrillation.

In the present study we also investigated the relative importance of cardiac rhythm itself—that is sinus rhythm versus atrial fibrillation—to the release of ir-ANP. The two groups investigated, with 13 patients in each, were almost identical in terms of several important echocardiographic cardiac variables. But the significantly higher concentration of ir-ANP in the atrial fibrillation group could not be explained by more pronounced dilatation of the left atrium because this variable was similar in both groups. Furthermore, no relation was found between left atrial dimensions and plasma concentration of ir-ANP in either of the two groups. Because the left atrial size varied considerably, significant correlations with plasma ir-ANP concentration should have been detected. This observation provides further evidence for the view that left atrial size, in clinically stable patients, is not a major determinant of the plasma concentration of ANP. The lack of a significant correlation between left atrial dimension and plasma ir-ANP accords with the findings in a previous study of 30 patients in sinus rhythm.[23] In

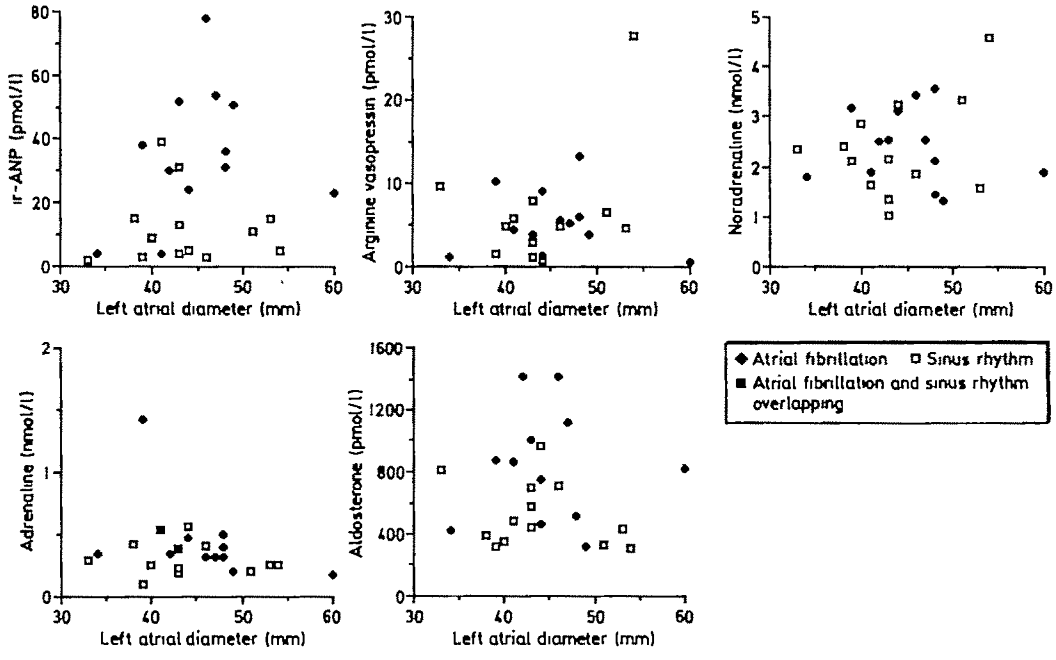

Figure 2 Relations between left atrial diameter and plasma concentrations of analysed hormones No significant correlations were found. Table 3 shows the correlation data. Missing values: aldosterone (one); arginine vasopressin (two); ir-ANP (two patients had values of 43 mm and 24 pmol/l).

Table 3 Correlation between echocardiographic measurements and hormone concentrations

	Sinus rhythm				*Atrial fibrillation*			
	LAD		*LAD/AO*		*LAD*		*LAD/AO*	
Variable	r^2	p	r^2	p	r^2	p	r^2	p
ir-ANP (pmol/l)	2×10^{-4}	0·96	0·01	0·70	0·07	0·38	0·18	0·15
Aldosterone (pmol/l)	0·09	0·31	0·01	0·83	2×10^{-4}	0·96	0·11	0·28
Adrenaline (nmol/l)	0·02	0·64	0·01	0·80	0·20	0·13	0·17	0·16
Noradrenaline (nmol/l)	0·13	0·23	0·13	0·23	0·01	0·79	3×10^{-4}	0·96
AVP (pmol/l)	0·17	0·19	0·18	0·17	0·01	0·74	0·02	0·69

AO, aortic root diameter, AVP, arginine vasopressin; LAD, left atrial diameter.

another study an unchanged left atrial diameter, measured by means of echocardiography, before, one, and 30 days after successful cardioversion treatment for short term atrial fibrillation was associated with a considerable and significant decrease in the plasma concentration of ir-ANP.[8]

Absence of a correlation between the left atrial diameter and the plasma concentration of ir-ANP is not a surprising finding in view of the complexity of the neurohormonal changes caused by a hypokinetic circulation and atrial stretch.[24] Probable modulating factors such as atrial compliance and transmural pressure might also reduce the value of echocardiographic measurements of the left atrium as an indication of actual dynamic distension of the atria. The possibility of resetting of at least some atrial receptors or a fall in sensitivity with chronic dilatation might also have influenced our results.[25]

In contrast with our findings, in a study on children with congenital heart disease an index calculated as the right atrial area in relation to body area was found to correlate well with plasma concentrations of ANP.[26] It is reasonable to expect that factors modulating ANP release and atrial stretch will be less pronounced in this younger patient group with well-defined cardiac disease, making the postulated relation between atrial pressure and atrial size more easily detectable.

Plasma concentrations of adrenaline, noradrenaline, and arginine vasopressin were similar in both the groups and these hormone concentrations did not correlate with the left atrial measurements. Raised plasma concentrations of noradrenaline, adrenaline, and arginine vasopressin were reported during hypokinetic circulation.[24 27] The lack of difference in these variables emphasises the similarity between the two patient groups. Furthermore, the concentrations of these vasoactive hormones were close to the normal ranges, indicating that there was no major degree of derangement of the peripheral and renal circulations. Hence, an increased plasma ir-ANP concentration seems to be a very sensitive marker of atrial stretch, which is probably associated with atrial fibrillation.

Some studies suggest that the heart rate per se influences the release of ANP but other studies of atrial pacing and of patients with congestive heart failure showed no clear correlation between plasma ir-ANP and heart rate. A higher heart rate in the atrial fibrillation group is not a likely cause of the raised ir-ANP because the heart rates were almost equal in both groups. The possibility that the dynamic pressure changes within the cardiac cycle and variability of pressure changes from beat to beat influenced the release of ANP cannot be ruled out. Furthermore, a difference in the relation between atrial pressure and atrial wall stretch between patients in atrial fibrillation and those in sinus rhythm, which might be attributable to the presence or absence of atrial contraction, is likely. A study comparing the influence of DDD and VVI pacing on plasma concentrations of ir-ANP in patients with type III atrioventricular block supports the view that irregularities in ventricular rhythm, with loss of the synchronous atrial contractions, may lead to disadvantageous atrial stretching.[28] VVI pacing was associated with raised concentrations of ir-ANP, whereas the plasma concentrations were normal in the group with DDD pacing. The importance of trying to find the most physiological pacing mode was shown in a study in which a lower cardiovascular morbidity and mortality was found among patients with sick sinus syndrome treated with AAI pacing than in those treated with VVI pacing.[29] Since the plasma concentrations of ir-ANP seem to be a sensitive marker of atrial distension, with a rapid responsiveness to changes in such distension, they might be of some use as a guide in optimising pacemaker treatment.

Information is limited on the effects of calcium entry blocking agents on renal haemodynamic function and plasma concentrations of aldosterone in patients with atrial fibrillation and mild compensated congestive heart failure. In some patients with congestive heart failure nifedipine can cause deterioration of renal function.[30] However, in the present study only four patients in the atrial fibrillation group were treated with calcium blockers and data on individual differences between these pairs of patients do not account for the observed statistically significant difference between the groups. Normal electrolytes and similar diuretic treatment in the examined groups make these factors less plausible as causes of the difference. Hence, it is possible that the difference in the plasma aldosterone concentration reflects unfavourable changes in haemodynamic function during atrial fibrillation.

We conclude that atrial fibrillation is associated with an increase in the plasma concentrations of ir-ANP and aldosterone that is independent of left atrial dimensions, age, and heart rate. These findings do not deviate from the previous observation that atrial stretch, as reflected by atrial mean pressures, is the major stimulus for release of ANP, but they underscore the difficulties in correlating echocardiographic assessments of patients with plasma concentrations of cardiovascular hormones. We do not know whether our findings can be fully explained by unfavourable haemodynamic conditions in the atria (as reflected by raised mean atrial pressures) or are influenced by irregularities in atrial stretch caused by irregular ventricular contractions, or are attributable to a yet unknown link between atrial fibrillation and plasma ANP. To clarify this issue further, we need studies focusing on the atrial contraction pattern in relation to haemodynamic changes and hormone release. In addition, the present findings indicate that aldosterone is a highly sensitive indicator of alterations in haemodynamic function during atrial fibrillation.

1 de Bold AJ, Borenstein HB, Veress AT, Sonnenberg H. A rapid and potent natriuretic response to intra-venous injection of atrial myocardial extract in rats. *Life Sci* 1981;28:89–94.

2 Mancini GBJ, McGillem MJ, Bates ER, Weder AB, DeBoe SF, Grekin RJ. Hormonal responses to cardiac tamponade inhibition of release of atrial natriuretic factor despite elevation of atrial pressures. *Circulation* 1987;76.884–90

3 Gellai M, DeWolf RE, Kinter LB, Beeuwkes R III. The effect of atrial natriuretic factor on blood pressure, heart rate, and renal functions in conscious, spontaneously hypertensive rats. *Circ Res* 1986,59:89–94.

4 Winquist RJ. The relaxant effects of atrial natriuretic factor on vascular smooth muscle. *Life Sci* 1985,37·1081–7.

5 Anderson JV, Struthers AD, Payne NN, Slater JDH, Bloom SR. Atrial natriuretic peptide inhibits the aldosterone response to angiotensin II in man *Clin Sci* 1986;70 507–12

6 Nicklas JM, DiCarlo LA, Koller PT, *et al*. Plasma levels of immunoreactive atrial natriuretic factor increase during supraventricular tachycardia. *Am Heart J* 1986;112. 923–8

7 Roy D, Paillard F, Cassidy D, *et al*. Atrial natriuretic factor during atrial fibrillation and supraventricular tachycardia *J Am Coll Cardiol* 1987,9:509–14.

8 Petersen P, Kastrup J, Vilhelmsen R, Schutten HJ. Atrial natriuretic peptide in atrial fibrillation before and after electrical cardioversion therapy. *Eur Heart J* 1988;9·639–41.

9 Petersen P, Kastrup J, Brinch K, Godtfredsen J, Boysen G. Relation between left atrial dimension and duration of atrial fibrillation. *Am J Cardiol* 1987;60.382–4.

10 Ingram RH, Braunwald E Classification of pulmonary edema. In. Braunwald E, ed *Heart disease vol. 1* 3rd ed. Philadelphia WB Saunders, 1988.553–4.

11 Jonsell S. A method for the determination of the heart size by teleroentgenography (a heart index). *Acta Radiol (Stockh)* 1939;29 325–40.

12 Sahn DJ, DeMaria A, Kisslo J, Weyman A. Recommendations regarding quantitation in M-mode echocardiography: results of a survey of echocardiographic measurements *Circulation* 1978;58 1072–83.

13 Feigenbaum N. *Echocardiography* 4th ed. Philadelphia. Lea and Febiger, 1986:127 and 171.

14 Theodorsson-Norheim E, Hemsén A, Brodin E, Lundberg JM Sample handling techniques when analyzing regulatory peptides *Life Sci* 1987,41:845–8.

15 Edwards CRW. Vasopressin In· Gray CH, James VHT, eds. *Hormones in blood* New York: Academic Press, 1979 423–50.

16 Jacobson SH, Eklof O, Eriksson CG, Lins L-E, Tidgren B, Winberg J Development of hypertension and uraemia after pyelonephritis in childhood. 27 year follow up *Br Med J* 1989,299 703–6

17 Bayard F, Beitins IZ, Kowarski A, Migeon CJ. Measurement of aldosterone by radioimmunoassay. *J Clin Endocrinol Metab* 1970,31.1–6.

18 Mayes D, Furuyama S, Kem DC, Nugent CA A radioimmunoassay for plasma aldosterone. *J Clin Endocrinol Metab* 1970;30 682–5.

19 Hallman H, Farnebo L-O, Hamberger B, Jonsson G A sensitive method for the determination of plasma catecholamines using liquid chromatography with electrochemical detection. *Life Sci* 1978;23 1049–52.

20 Hjemdal P, Daleskog M, Kahan T. Determination of plasma catecholamines by high performance liquid chromatography with electrochemical detection: comparison with a radioenzymatic method. *Life Sci* 1979;25 131–8.

21 Burnett JC Jr, Kao PC, Hu DC, *et al* Atrial natriuretic peptide elevation in congestive heart failure in the human *Science* 1986,231.1145–7.

22 Crozier IG, Ikram H, Nicholls MG, Espiner EA, Yandle TG. Atrial natriuretic peptide in spontaneous tachycardias. *Br Heart J* 1987,58.96–100.

23 Crozier IG, Nicholls MG, Ikram H, Espiner EA. Relation between left atrial diameter and plasma atrial natriuretic peptide, renin and vasopressin. *Am J Cardiol* 1986; 58·1134–6

24 Levine TB, Francis GS, Goldsmith SR, Simon AB, Cohn JN Activity of the sympathetic nervous system and renin-angiotensin system assessed by plasma hormone levels and their relation to hemodynamic abnormalities in congestive heart failure. *Am J Cardiol* 1982;49·1659–66.

25 Francis GS Neurohumoral mechanisms involved in congestive heart failure. *Am J Cardiol* 1985;55.15A–21A.

26 Ross RD, Daniels SR, Dolan LM, Young CA, Meyer RA. Determinations of plasma atrial natriuretic factor concentrations in congenital heart disease. *Am J Cardiol* 1988, 62 785–8

27 Share L. Role of arginine vasopressin in cardiovascular regulation. *Physiol Rev* 1988;68.1248–84.

28 Vardas PE, Travill CM, Williams TDM, Ingram AM, Lightman SL, Sutton R Effect of dual chamber pacing on raised plasma atrial natriuretic peptide concentrations in complete atrioventricular block. *Br Med J* 1988;296 94.

29 Rosenqvist M, Brandt J, Schuller H Long-term pacing in sinus node disease effects of stimulation mode on cardiovascular morbidity and mortality. *Am Heart J* 1988;116: 16–22

30 Diamond JR, Cheung JY, Fang LS. Nifedipine-induced renal dysfunction. *Am J Med* 1984;77 905–9.

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Antianginal efficacy of exercise training: a comparison with β blockade

Iain C Todd, David Ballantyne

Abstract

Forty men with chronic stable angina and no prior myocardial infarction were studied. Exercise tolerance testing was carried out off treatment and after β blockade. β Blockers were stopped and the patients were randomised to a control group and a study group of patients who undertook a one year high intensity training programme. The groups were then restudied. Submaximum heart rate was reduced by 13 beats per minute by training and by 23 beats per minute by atenolol. Training increased the maximum heart rate by 10 beats per minute and atenolol reduced it by 29 beats per minute. The double produce ST threshold was increased from 183 to 205 by training but reduced to 143 by atenolol. Maximum ST depression was similarly reduced by both training and atenolol. As a result of the effects on maximum heart rate, training produced a greater improvement in exercise tolerance than atenolol with a treadmill time increased from 741 seconds to 1272 seconds with training compared with 974 seconds with atenolol. Other variables were similarly affected.

Thus the antianginal efficacy of exercise training is as good as that achieved by β blockade and represents an alternative to such treatment.

Exercise training may be used as an adjunct to medical treatment in the management of coronary artery disease. It has been shown to aid the rehabilitation of patients after myocardial infarction[1-3] or coronary artery bypass grafting[4-6] and will also improve exercise tolerance in chronic stable angina pectoris.[7-11] This latter effect is achieved by a reduction in heart rate at submaximal workloads and hence an increase in the level of work required to reach the angina threshold. The relative bradycardia is the result of a reduced level of sympathetic stimulation and in the resting state also an increase in parasympathetic tone. This in turn is brought about by a reduction in sensory input to the cardiovascular control centre in the medulla oblongata by receptors in trained muscles.

β Blockade competitively inhibits the sympathetic stimulation of the heart and, like exercise training, produces a relative bradycardia. The similarity in the modes of action of exercise training and β blockade prompted us to compare these two methods of reducing sympathetic stimulation and improving exercise tolerance. Whereas others examined the effectiveness of training during β blockade,[12-15] the effects of the two interventions had not been directly compared.

Patients and methods

We studied 40 men aged <60 years with chronic stable angina of at least six months' duration. Exclusion criteria included previous myocardial infarction, diabetes, valve disease, hypertensive left ventricular hypertrophy, and exercise induced ventricular arrhythmias. Treatment with β blockers was stopped for four weeks before the study. An initial treadmill exercise tolerance test for diagnosis and familiarisation was carried out. This was followed one week later by a baseline exercise test. The diagnosis of angina required a typical history of exertional chest pain and the development of such pain during the initial exercise tolerance test in association with horizontal or downsloping ST depression of >1 mm recorded 80 ms after the J point. All patients then received atenolol 100 mg daily for one week with repeat exercise tolerance testing thereafter. Atenolol was then withdrawn and patients were randomised into exercise and control groups to control for the effect of the natural course of the disease on exercise tolerance.

Over the next year all patients requiring antianginal medication received nifedipine and glyceryl trinitrate in the first instance with the later addition, if required, of isosorbide dinitrate. When β blockade was required during the study for increasing symptoms then the patient was withdrawn from the study. Twenty patients were randomised into each group. During the course of the study unstable angina requiring β blockade developed in one patient in the exercise group, and one patient in the control group died suddenly. Two other patients in each group were lost to follow up. At the end of the year we restudied 17 patients in each group.

EXERCISE TESTING

Exercise testing was carried out using the Marquette Case II treadmill with continuous 12 lead electrocardiographic monitoring. The electrocardiogram was recorded in patients sitting and standing at rest and at one minute intervals throughout the test. A modified Naughton protocol was used with a constant speed of 3 mph (5 km/h) and initial gradient

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Table 1 Demographic data on exercise group

Patient	*Age*	*Duration of angina (month)*	*Smoking habits*	*Height (in)*	*Weight (lb)*
1	51	24	Ex-smoker	74	220
2	55	8	Ex-smoker	70	175
3	47	10	Non-smoker	69	190
4	45	24	Ex-pipe smoker	70	188
5	57	6	Ex-smoker	68	165
6	55	12	Ex-smoker	64	142
7	60	36	Ex-smoker	68	136
8	51	6	Ex-smoker	72	221
9	52	9	Smoker	64	159
10	55	60	Smoker	74	198
11	52	8	Smoker	74	215
12	60	24	Non-smoker	70	188
13	48	6	Ex-smoker	68	148
14	59	18	Non-smoker	67	140
15	57	108	Non-smoker	67	150
16	58	6	Non-smoker	68	196
17	48	12	Smoker	68	192
18	46	12	Ex-smoker	69	204
19	48	6	Non-smoker	67	182
20	58	6	Ex-smoker	72	220
Mean (SD)	53	20 0 (24·6)	—	69 (3)	182 (28)

1 inch = 25·4 mm; 1 lb = 0 45 kg.

of 0%.[16] The gradient was increased by 2·5% every three minutes. All exercise tests were carried out between 9 am and 10 am after a 12 hour fast and 24 hours after the last dose of any antianginal agent. Blood pressure was recorded manually during the last minute of each stage of the exercise protocol. Heart rate and ST segment variables were measured from the appropriate 12 lead electrocardiograms. The treadmill protocol produced a linear increase in workload and heart rate, the rate of change of each being 1 MET and 4–5 beats per stage respectively. This allowed accurate measurement of end points. We examined three broad groups of variables: *(a)* those which reflect "fitness"—that is resting and submaximal heart rates; *(b)* those which reflect disease severity—that is maximum heart rate, maximum double product (heart rate × systolic pressure), maximum ST depression, and double product ST threshold (double product at which 1 mm of horizontal or downsloping ST depression was first recorded); and *(c)* those that reflect a combination of fitness and disease severity—that is treadmill time, estimated workload, and time to 1 mm ST depression.

Table 2 Demographic data on control group

Patient	*Age (yr)*	*Duration of angina (month)*	*Smoking habits*	*Height (in)*	*Weight (lb)*
21	57	8	Non-smoker	62	127
22	60	96	Non-smoker	73	191
23	54	10	Ex-smoker	69	187
24	50	12	Smoker	70	175
25	55	6	Non-smoker	67	166
26	48	15	Non-smoker	68	181
27	53	10	Ex-smoker	71	190
28	53	6	Ex-smoker	73	225
29	56	6	Non-smoker	68	170
30	48	6	Ex-smoker	71	184
31	40	8	Ex-smoker	70	214
32	53	12	Smoker	70	205
33	49	6	Smoker	66	159
34	60	9	Non-smoker	68	170
35	37	6	Smoker	66	181
36	56	6	Ex-smoker	68	165
37	50	12	Smoker	66	143
38	46	6	Ex-smoker	68	171
39	45	8	Non-smoker	70	216
40	50	6	Ex-smoker	68	190
Mean (SD)	51	12·7 (9·8)	—	69 (3)	181 (24)

1 inch = 25 4 mm; 1 lb = 0 45 kg.

TRAINING SCHEDULE

The training group undertook the Canadian Airforce Programme for Physical Fitness.[17] It is a brief (11 minutes) daily exercise programme of five callisthenic type exercises that needs no special equipment. It could therefore be prescribed for daily home use. Exercise levels increase in intensity each week to achieve a progressive increase in physical fitness. Patients were advised to progress from one level to the next provided the previous level could be completed within 11 minutes without excessive chest pain or dyspnoea. A weekly in-hospital supervised session was used to initiate new patients and to monitor early progress. Subsequent attendance at this session was optional. In-hospital sessions were carried out under the guidance of physiotherapists. Those individuals in the control group were informed that mild exercise could be beneficial and were advised on diet and smoking habits. Regular follow up of these patients was maintained throughout the year.

Results

Tables 1 and 2 show the demographic data for the two groups. The mean age for the exercise group was 53 (range 45–60) with a mean duration of angina of 20·0 months, while the mean age for the controls was 51 (range 37–60) with a mean duration of angina of 12 7 months. There was a low overall incidence of smoking although many patients were former smokers, most having stopped since diagnosis.

Randomisation produced groups whose baseline measurements differed statistically in only one respect. The mean (SD) maximum ST depression for the control group (1·5 (0·8) mm) was significantly less than that for the exercise group (1·9 (0·9) mm). Quite large variations in other variables were, however, not statistically significant. Most notable among these differences was the time to 1 mm ST depression, which was twice as long in the controls as in the exercise group. The overall trend was for the exercise group to be less fit, as judged by resting and submaximal heart rate, and to have more severe disease, judged by maximum heart rate and double product, maximum ST depression, and double product ST threshold. As a result the combined variables of performance showed a trend for poorer performance among the exercise group at the outset. These trends are most important when one considers the extent of change after training since one might postulate that irrespective of training effect the extent of change might be proportional to severity of abnormality at the outset. It was important therefore to examine this relation. Figure 1 shows the time to 1 mm ST depression plotted against change in time to 1 mm of ST depression. For this and all other variables no linear relation was found. The end point for all patients on baseline exercise testing was the development of angina.

Table 3 shows the effects of training and atenolol on the measured treadmill variables

Table 3 Effect of training and atenolol on variables of treadmill performance

	Exercise group			*Control group*	
	Baseline (mean (SD))	*Atenolol (mean (SD))*	*One year (mean (SD))*	*Baseline (mean (SD))*	*One year (mean (SD))*
Resting HR	81 (12)	64 (8)	76 (10)	74 (10)	75 (9)
Stage I HR	111 (19)	88 (11)	98 (15)	106 (16)	102 (10)
Stage II HR	116 (19)	93 (13)	103 (16)	110 (18)	106 (10)
Max HR	128 (17)	109 (12)	138 (21)	136 (22)	134 (24)
Max DP	219 (55)	164 (44)	244 (67)	259 (74)	248 (74)
DP ST threshold	183 (51)	143 (43)	205 (64)	227 (75)	206 (60)
Max ST depression	1·9 (0·9)*	1·6 (1·0)	1·6 (1·2)	1·5 (0·8)*	1·4 (0·8)
Time to 1 mm ST dep	374 (369)†	749 (439)	881 (668)	719 (560)	715 (580)
Log time to 1 mm ST dep	2·37 (0·44)	—	—	2·68 (0·46)	—
Treadmill time (s)	741 (356)	974 (430)	1272 (514)	1006 (504)	1010 (546)
Workload (METS)	6·3 (1·9)	7·6 (2·2)	9·5 (2·9)	7·8 (2·8)	8·0 (3·1)

DP, double product, HR, heart rate
*p < 0·05
†Non-normal data by "goodness of fit" test

for the exercise group and the baseline and one year values for the control group. The reduction in resting and submaximal heart rate achieved by training was not as great as that achieved by β blockade. β Blockade with atenolol clearly reduces resting heart rate in particular. This fell by a mean of 5 beats during training and 17 beats during β blockade. During exercise, however, the difference was less pronounced and the three lines were parallel (fig 2). Training reduced stage I and II heart rates by 13 beats while atenolol reduced them by 23 beats. Figure 3 summarises the results of those variables that reflect disease severity. On maximal exercise, training produced an increase in mean (SD) maximum heart rate from 128 (17) beats per minute to 138 (21) beats per minute (p < 0·05), while with β blockade maximum heart rate was reduced to 109 (12) beats per minute (p < 0·001). Similarly, the maximum double product was increased by training from 219 (55) to 244 (67) (p < 0·05) and reduced by atenolol to 164 (44) (p < 0·001). The submaximal measure of disease severity, the double product ST threshold, was also increased by training from 183 (51) to 205 (64) but reduced by atenolol to 143 (43). Both training and atenolol reduced the maximum ST depression by similar amounts (1·9 (0·9) mm at baseline, 1·6 (1·0) mm for atenolol and 1·6 (1·2) after training) (p < 0·05).

The combined variables of treadmill performance shown in fig 4 showed that both atenolol and training produced large improvements in time to 1 mm ST depression, treadmill time, and treadmill workload. Atenolol increased time to 1 mm ST depression by 100% (374 (369) *v* 749 (439) s) but training produced a 136% increase in this variable to 881 (668) s. Similarly, treadmill time was increased from 741 (356) to 974 (430) s by atenolol (31% increase; p < 0·001) but to 1272 (514) s by training (72% increase; p < 0·001). Treadmill workload increased from 6·3 (1·9) METs to 7·6 (2·2) METs with atenolol and to 9·5 (2·9) METs with training. The improvements in these variables achieved by exercise training were significantly better than those achieved by β blockade. During β

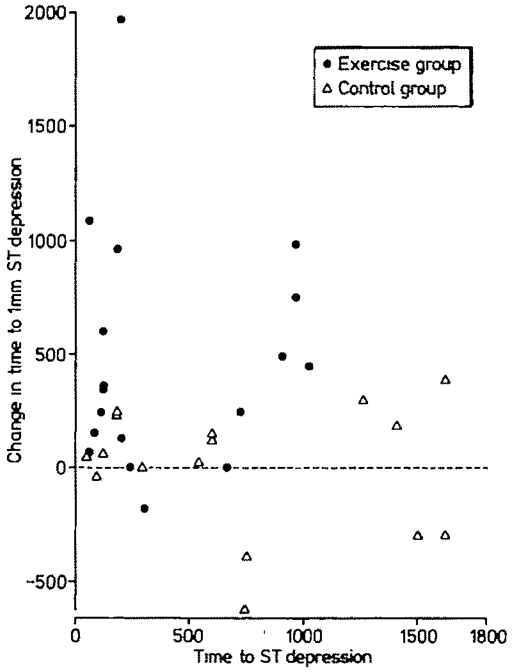

Figure 1 Graph of baseline time to 1 mm ST depression against interval change in time to 1 mm ST depression. Six patients did not complete the study.

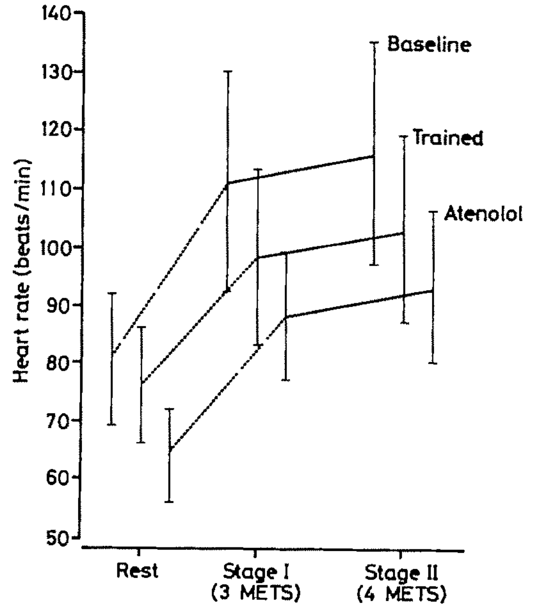

Figure 2 Graph of mean heart rate against stage of treadmill protocol for the exercise group at baseline after β blockade and after training.

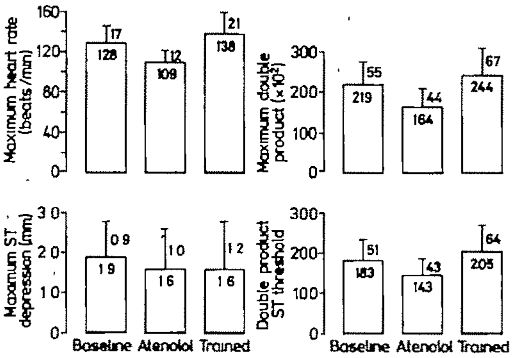

Figure 3 Treadmill measures of disease severity: effect of training or atenolol.

blockade all patients except one exercised to angina. The one exception stopped because of exhaustion. After training this patient and one other exercised to exhaustion without angina. Two other patients were stopped because of ST depression of > 3 mm after training with only mild chest discomfort. Both had similar degrees of ST depression at baseline but with severe anginal pain.

All patients in the exercise group noted an improvement in their symptoms within 6–8 weeks of starting training. At one year six patients were symptom free during normal daily activities. These six and two others had stopped taking all antianginal agents except sublingual glyceryl trinitrate. No patient had increased drug treatment apart from the patient with unstable angina who was withdrawn from the study. Only two further patients in the exercise group and one control patient stopped smoking during the study period. There was a trend towards a reduction in weight in the exercise group over the study period, but this was not significant. Though this was not studied in detail the impression of the patients was that "fat" around the waistline was replaced by "muscle" around the chest.

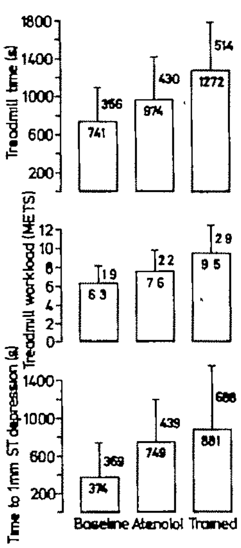

Figure 4 Combined treadmill performance measures: effect of training or atenolol.

Discussion

A reduction in the chronotropic response to exercise is the basis for improved exercise tolerance in "fit" or trained individuals. In patients with angina pectoris whose exercise tolerance is limited by myocardial ischaemia at a fixed heart rate this training effect can result in significant improvements in exercise capacity. In men following a short once daily exercise programme we found improvements in submaximal heart rate as great as in men following the more usual regimens of several lengthy sessions per week—heart rate in stage I and stage II was reduced by 13 beats per minute compared with a reduction of 14 beats per minute achieved by Nolewadjka *et al* using gymnasium exercise to 60–70% of maximum heart rate for five hour long sessions per week over a seven month period.[18] The same degree of reduction was found by Ehsani *et al* using jogging and bicycle ergometry for similar periods each week up to 80–90% of $\dot{V}O_2$ max over a year.[19]

We also compared the response to exercise with that to high dose β blockade, a treatment that mimics the effect of fitness on heart rate. We chose atenolol as one of the most commonly used β blockers and a dose of 100 mg as the generally recommended dose and one which, in our experience, results in a considerable reduction in resting and submaximal heart rate. Our training programme produced a reduction in submaximal heart rate that was 57% of that achieved by 100 mg of atenolol. This in itself would compare favourably with the more modest degree of β blockade achieved by many alternative drug regimens. Many of these young patients complained of side effects on high dose atenolol, such as lethargy and cold extremities, that would have merited a dose reduction. On the basis of its effect on submaximal heart rate alone therefore we believe that training is a realistic alternative to β blockade.

While reductions in submaximal heart rate result in improved exercise tolerance and less angina it is important to look also at the effect of these two modes of treatment on maximal heart rate. β Blockade reduces the angina threshold indicating a deleterious effect on the balance between myocardial oxygen supply and demand.[20 21] It has been postulated that increased left ventricular volume increases wall tension and hence myocardial oxygen demand, causing a reduction in maximal heart rate. It has also been suggested that reduced contractility may be responsible. A previous report from this department[22] supports the alternative explanation of reduced distal coronary artery flow in the presence of β blockade. Whatever the mechanism, the effect is to reduce the improvement in exercise tolerance that would be expected from the reduction in submaximal heart rate. Our study again confirms this finding. No such effect occurs with exercise training and most studies show either no change or a rise in maximal heart rate, the latter being more likely if training is continued for long periods. Our study with a training period of one year produced an 8% increase in maximum heart rate and an 11% increase in maximum double product. During the same period there were small reductions in these variables in the control group. An increase in double product implies an increase in myocardial oxygen consumption assuming that there is no reduction in the wall tension or contractility variables that also affect myocardial oxygen consumption. Because endurance training causes left ventricular dilatation, however, this would tend, if anything, to increase wall tension. Evidence from other studies also suggests that contractility on maximal exercise is likely to be increased or unchanged.[23 24]

One of the earliest studies to show a rise in maximum heart rate and triple product (heart rate × systolic blood pressure × ejection time) was reported by Redwood *et al* in 1972.[8] After only six weeks' training they showed a 13·4% increase in triple product. All patients in their study had angina and exercise training was carried out at an intensity sufficient to produce angina. Redwood suggested that the increase in myocardial oxygen consumption may indicate improved myocardial perfusion. Alternatively, alterations in the haemoglobin oxygen dissociation curve may allow a greater release of oxygen to the myocardium or trained individuals may simply have a higher pain threshold.

With the exception of Sim and Neil in 1974[9] most studies carried out over the next decade showed no improvement in maximum heart rate or double product.[18,25,26] This failure may have been related to the trend toward lower levels of exercise over this period of time. It was the aim of all of these studies to maintain exercise below the ischaemic threshold. During the past decade, however, several workers have again reported an increase in maximum heart rate and double product.[10,11,19,27-30] While most of these studies have concentrated on the assessment of left ventricular function or perfusion, some have considered other electrocardiographic criteria of disease severity. In the study reported here maximum ST depression fell from 1·9 (0 9) mm to 1·6 (1·2) mm despite an 11% increase in maximum double product. Ehsani *et al* reported very similar figures in a small group of patients on a one year high intensity programme.[19] Such a reduction in ST depression makes it unlikely that decreased pain threshold is responsible for the improved maximum heart rate. Further weight is lent to this view by the 12·6% improvement in double product ST threshold in the training group compared with a 7·5% deterioration in the controls over the same period. Though neither result quite achieves statistical significance, an intergroup comparison of the interval change shows a significant difference between those who trained and those who did not ($p < 0{\cdot}02$). Ehsani *et al's* study also showed a 22% improvement in this variable.

Raffo *et al* and Winter *et al* studied patients on the Canadian Airforce PBX schedule in Leeds.[10,29] The initial paper reported a six month study of 12 patients on the programme and 12 controls, while the second study looked at longer periods of training in nine of the original 12, in addition to a further eight patients. They did not measure symptom limited exercise tolerance but did report improvements in heart rate, ST threshold, and double product ST threshold. As in the study reported here, improvements in these variables were found in the training group with deteriorations in the controls. Like our own study, all of these studies used exercise of relatively high intensity in patients with ischaemic ST depression and angina pectoris. The conclusions of both groups are similar. The finding of less ST depression at the same or greater cardiac workload implies better myocardial oxygenation, either secondary to improved myocardial perfusion or to improvements in oxygen delivery systems. This study broadly accords with these conclusions.

The divergent effects of β blockade and training on maximum heart rate mean that, despite a lesser degree of blunting of the heart rate response to exercise, training does in fact produce a greater improvement in exercise tolerance and work capacity than β blockade as measured by combined variables. It might be argued that we made an unfair comparison between one week's β blockade and one year's exercise training. There is, however, no evidence to suggest that long periods of β blockade result in further improvements in exercise tolerance. Indeed on theoretical grounds one might expect that the converse would occur. Autoregulation of β receptors might indeed reduce the effectiveness.

We did of course compare the efficacy of training with trough concentrations of atenolol in that the exercise tests were carried out 24 hours after the last dose. We recognise the attenuation of submaximal heart rate was greater three hours after atenolol administration than 24 hours after. On the negative side, however, there is a greater reduction in maximum heart rate.[31] Published data on the peak and trough efficacy of various doses of atenolol showed that a dose of 100 mg resulted in a 28% improvement over placebo in treadmill time at three hours compared with a 20% improvement at 24 hours.[31] It is unlikely therefore that our improvement of 31% at 24 hours with atenolol would have been sufficiently better at three hours to surpass the 72% improvement with exercise training.

One weakness of this study was our failure, despite randomisation, to produce comparable groups at the outset of the study. While this is disappointing, the fact that our exercise group began with a poorer exercise tolerance than the controls and ended with a significantly better performance, highlights the effectiveness of this treatment. The men in the group whose disease was more severe were also less fit, suggesting that there is a link between disease severity and fitness—but what is cause and what effect is open to debate.

The exercise programme used in this study was deliberately chosen for its ease of use. Our patients found that its brief daily format is one which improves compliance. It requires no special equipment and is safely used unsupervised at home. It resembles drug treatment more than conventional time consuming hospital based programmes. We think that we have shown that it compares favourably with conventional drug treatment and that it merits serious consideration by all clinicians as an alternative to β blockade as an initial treatment in many patients with angina pectoris.

Our patients had relatively mild ischaemic heart disease—that is they were young with no permanent cardiac damage and could be maintained off β blockade. None the less, they were significantly limited by angina, experiencing on average two episodes of painful ischaemia per day at baseline and with a mean treadmill workload capacity of only 6·5 METS. Though the results in more severely affected groups are unknown we think that the same principles could be applied to other patients with ischaemic heart disease and may allow a reduction in antianginal treatment in all groups.

1 Frick MH, Katila M. Hemodynamic consequences of physical training after myocardial infarction. *Circulation* 1968;37 192–202.
2 American Heart Association Council on Scientific Affairs.

Physician supervised exercise programs in rehabilitation of patients with coronary heart disease. *JAMA* 1981;245 1463–6.

3 De Busk RF Physical conditioning following myocardial infarction. *Adv Cardiol* 1982;31·156–61.

4 Oldridge NB, Nagle FJ, Balke B, Cartiss RJ, Kahn DR. Aorto coronary bypass surgery: effects of surgery and 32 months of physical conditioning on treadmill performance. *Arch Phys Med Rehabil* 1978,59 268–75.

5 Murray GC, Beller GH. Cardiac rehabilitation following coronary artery surgery. *Am Heart J* 1983;105·1009–18

6 Froelicher V, Jensen D, Sullivan M A randomised trial of the effects of exercise training after coronary artery bypass surgery *Arch Intern Med* 1985;145.689–92.

7 Clausen JP, Larsen DA, Trap-Jensen JT. Physical training in the management of coronary artery disease. *Circulation* 1969;40 143–54

8 Redwood DR, Rosing DR, Epstein SE. Circulatory and symptomatic effects of physical training in patients with coronary artery disease and angina pectoris. *N Engl J Med* 1972;286:959–65.

9 Sim DN, Neil WA Investigation of the physiological basis for increased exercise threshold for angina pectoris after physical conditioning. *J Clin Invest* 1974,54 763–70.

10 Raffo JA, Luksic IV, Kappagoda CT, Mary DASG, Whitaker W, Linden RJ. Effects of physical training on myocardial ischaemia in patients with coronary artery disease *Br Heart J* 1980,43 262–9.

11 Ehsani AA, Biello DR, Schultz J, Sobel BE, Holloszy JO. Improvement of left ventricular contractile function by exercise training in patients with coronary artery disease. *Circulation* 1986;74 350–8

12 Pratt CM, Welton DE, Squires WG, *et al* Demonstration of training effect during chronic beta adrenergic blockade in patients with coronary artery disease *Circulation* 1987;64.1125–9.

13 Laslett LJ, Paumer L, Scott-Baier P, Amsterdam EA Efficacy of exercise training in patients with coronary artery disease who are taking propranolol. *Circulation* 1983,68:1029–34

14 Vahees L, Fagard R, Amery A. Influence of beta adrenergic blockade on the haemodynamic effects of physical training in patients with ischaemic heart disease. *Am Heart J* 1984;108·270–5.

15 Ehsani AA. Altered adaptive responses to training by nonselective beta adrenergic blockade in coronary artery disease *Am J Cardiol* 1986,58 220–4

16 Patterson JA, Naughton J, Pietras RJ, Gunnar RM. Treadmill exercise in assessment of the functional capacity of patients with cardiac disease *Am J Cardiol* 1972;30: 757–62.

17 *Physical fitness. Two series of exercises developed by the Royal Canadian Air Force.* Harmondsworth Penguin Books, 1973

18 Nolewadjka AJ, Kostuk WJ, Rechnitzer PA, Cunningham DA. Exercise and human collateralisation: an angiographic and scintigraphic assessment. *Circulation* 1979,60:114–20

19 Ehsani EA, Heath GW, Hagberg JM, *et al.* Effects of 12 months of intense exercise training on ischaemic ST-segment depression in patients with coronary artery disease *Circulation* 1981,64 1116–24

20 Goldbarg AN, Moran JF, Butterfield TK, *et al* Therapy of angina pectoris with propranolol and long acting nitrates. *Circulation* 1969,40 847–53

21 Dagenais GR, Pott B, Ross RS. Exercise tolerance in patients with angina pectoris. Daily variation and effects of erythrityl tetranitrate, propranolol and alprenolol *Am J Cardiol* 1971,28.10–6.

22 Todd IC, McGuinness JB, Ballantyne D Abolition of exercise induced ST depression after exercise training and its recurrence after β blockade *Br Heart J* 1988;59: 259–62.

23 Winder WW, Hagberg JM, Hickson RC, *et al* Time course of sympathoadrenal adaptation to endurance exercise training in man *J Appl Physiol* 1978,45 370–4.

24 Ehsani AA, Heath GW, Hagberg JM, *et al* Influence of exercise training on plasma catecholamines in patients with coronary artery disease [Abstract]. *Circulation* 1980,61(suppl III) 111–267

25 Clausen JP, Trap-Jensen J. Heart rate and arterial blood pressure during exercise in patients with angina pectoris: effects of training and of nitroglycerin. *Circulation* 1976,53·436–42

26 Dressendorfer RH, Smith JL, Amsterdam EA, Mason DT. Reduction of submaximal exercise myocardial oxygen demand post-work training program in coronary patients due to improved physical work efficiency. *Am Heart J* 1982;103·358–62

27 Jensen D, Atwood JE, Froelicher V, *et al.* Improvement in ventricular function during exercise studied with radionuclide ventriculography after cardiac rehabilitation. *Am J Cardiol* 1980,46·770–7.

28 Tubau J, Witztum K, Froelicher V, *et al.* Non invasive assessment of changes in myocardial perfusion and ventricular performance following exercise training. *Am Heart J* 1982,104.238–48

29 Winter C, Kardash MM, Whitaker W, *et al.* The effects of long-term physical training in patients with coronary heart disease. *Int J Cardiol* 1984;5 675–85.

30 Schuler G, Schlierf G, Wirth A, *et al.* Low-fat diet and regular supervised physical exercise in patients with symptomatic coronary artery disease reduction of stress-induced myocardial ischaemia. *Circulation* 1988,77. 172–81.

31 Jackson G, Schwartz J, Kates RE, *et al* Atenolol once daily cardioselective beta blockade for angina pectoris *Circulation* 1980,61 555–60

Br Heart J 1990;64:20–2

Ultrasound in the diagnosis of diaphragmatic paralysis after operation for congenital heart disease

Seshadri Balaji, Pavel Kunovsky, Ian Sullivan

Abstract

Phrenic nerve palsy is a recognised complication of operation for congenital heart disease in children. The accuracy of ultrasound in assessing diaphragmatic motion was prospectively compared with fluoroscopy in 16 patients in whom phrenic nerve palsy was suspected. Ultrasound successfully identified the five patients with phrenic nerve palsy; there were no false positive or false negative diagnoses.

Ultrasound was as effective as fluoroscopy in the diagnosis of abnormalities of diaphragmatic motion.

Diaphragmatic paralysis due to phrenic nerve injury may complicate as many as 10% of operations for complex congenital heart disease.[1] Though spontaneous recovery can be expected in about 85% of patients, it is associated with considerable morbidity, especially in children under the age of two years.[1] Early diagnosis and, when appropriate, surgical plication of the affected hemidiaphragm helps to reduce the time spent in intensive care and the duration of ventilatory assistance and is therefore an important part of the management.[2]

Fluoroscopy is the standard method of assessing diaphragmatic motion. Fluoroscopy, however, has disadvantages. The patient and staff are exposed to radiation. Also the patient, often still on ventilatory support, has to be moved to the fluoroscopy screening room with monitoring and infusion lines in place. This is potentially dangerous as well as being time and labour consuming. In contrast, ultrasound scanning with portable equipment can identify abnormalities of diaphragmatic motion at the bedside. We therefore prospectively studied patients with suspected diaphragmatic palsy after operation for congenital heart disease by both techniques to compare their diagnostic accuracy.

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Patients and methods

PATIENTS

Between 1 August and 1 December 1989, diaphragmatic palsy was suspected in 16 patients, aged 1 day to 8 years (median 8 months) from a total of 228 children who underwent operation for congenital heart disease at the Hospital for Sick Children, London. Indicators of possible diaphragmatic palsy were failure to be weaned from assisted ventilation at a time considered appropriate for the child, a raised hemidiaphragm on the chest radiograph, an asymmetric breathing pattern, or recurrent unilateral lung collapse. Table 1 lists the operations performed on these patients. The time between operation and diaphragmatic screening ranged from 2 to 24 days (mean (SD) 8 (6) days).

Table 1 Operations in children with suspected diaphragmatic palsy

Operation	*Number*
Repair of tetralogy of Fallot	5
Pulmonary artery banding	2
AVSD repair	2
Right MBTS	1
Truncus arteriosus repair	1
Fontan procedure	1
PA,IVS PV, left MBTS	1
DORV repair	1
RPA from aorta repair	1
Resection of coarctation	1

AVSD, complete atrioventricular septal defect, DORV, double outlet right ventricle; PA,IVS, pulmonary atresia, intact ventricular septum; PV, pulmonary valvotomy; RPA, right pulmonary artery; MBTS, modified Blalock-Taussig shunt

METHODS

Ultrasound assessment was performed by one investigator (SB) without knowledge of the results of fluoroscopic examination, which was performed by a different operator on the same day. An Advanced Technology Laboratories (ATL) Ultramark 4 ultrasound scanning machine was used with 7·5, 5, or 3 MHz mechanical sector scanheads as appropriate to the size of the child. Subcostal views (fig 1) with the transducer angled superiorly and posteriorly from the subxiphoid region at the midline, parasagittal views with the transducer at the lower costal margin in the midclavicular line, and coronal views (fig 2) with the transducer at the mid-axillary line were obtained in each case. Fluoroscopy was performed by anteroposterior screening of the thorax in the cardiac catheterisation laboratory.

All patients except one were on ventilatory assistance at the time of assessment. The ventilator was turned to the continuous positive airways pressure mode during the brief time required for each examination. The phases of respiration were timed by the operator placing a hand on the patient's chest during the examination. Paralysis of a hemidiaphragm was diagnosed if there was upward movement or absence of movement during inspiration (fig 3).

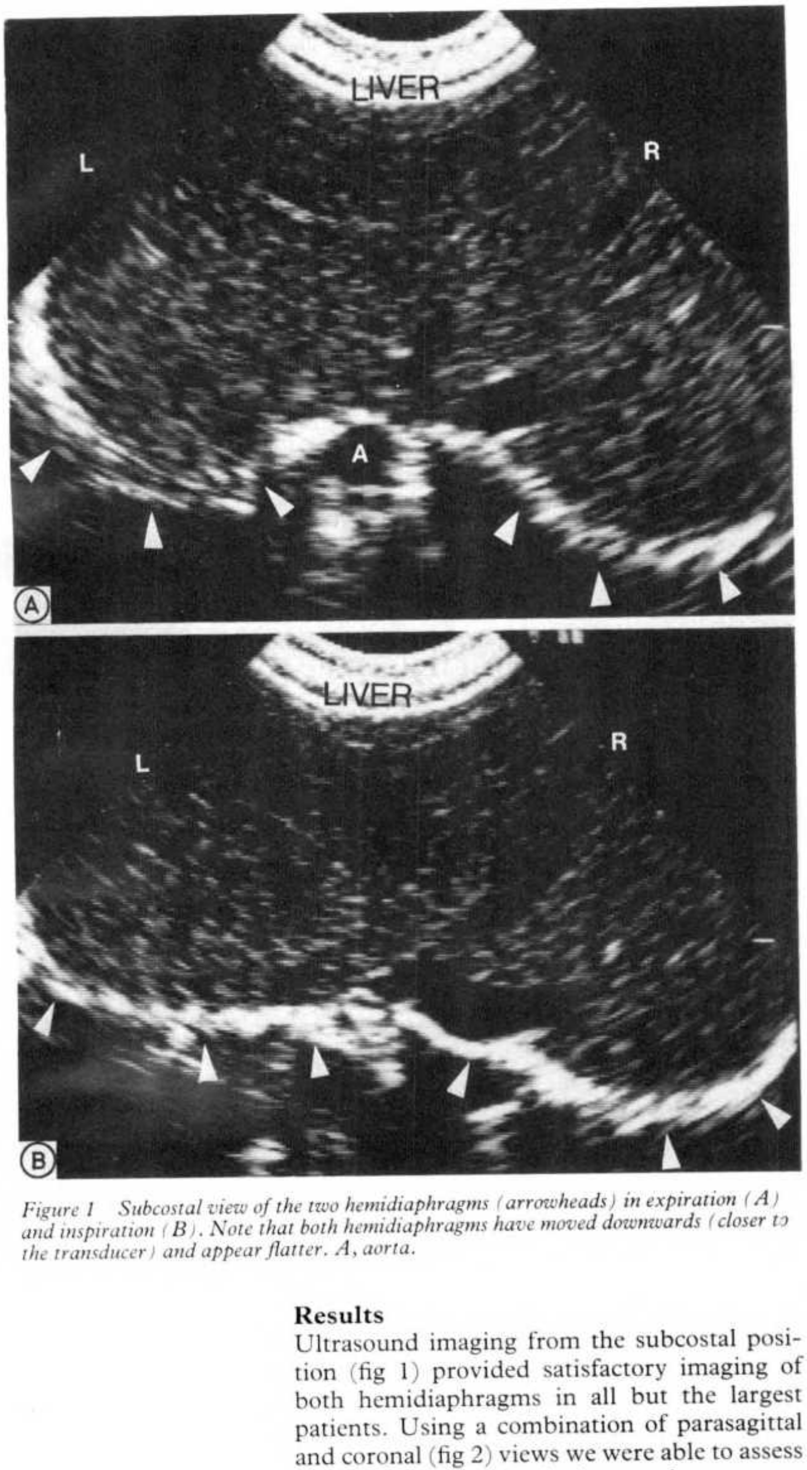


Figure 1 Subcostal view of the two hemidiaphragms (arrowheads) in expiration (A) and inspiration (B). Note that both hemidiaphragms have moved downwards (closer to the transducer) and appear flatter. A, aorta.

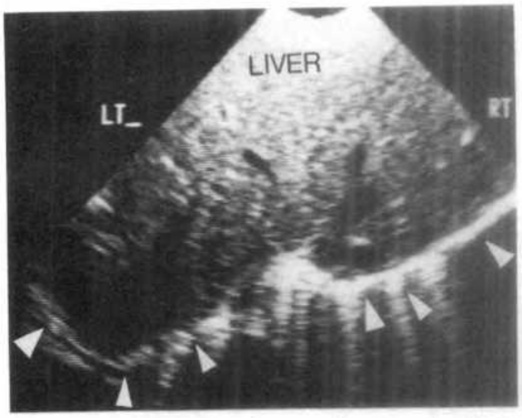


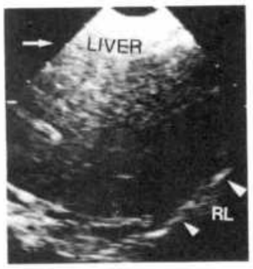
Figure 3 Subcostal view from a patient (case 1, table 2) with paralysed left hemidiaphragm. The right hemidiaphragm has contracted and is flat while the left side has moved upwards—there is paradoxical motion away from the transducer.

Results

Ultrasound imaging from the subcostal position (fig 1) provided satisfactory imaging of both hemidiaphragms in all but the largest patients. Using a combination of parasagittal and coronal (fig 2) views we were able to assess diaphragmatic motion in these patients.

Paralysis of the left hemidiaphragm was diagnosed in five patients—four after repair of tetralogy of Fallot and one after banding of the pulmonary trunk. Three patients required plication before extubation could be achieved (table 2). Two patients (aged 15 and 22 months) were successfully weaned from assisted ventilation despite paralysis of the left hemidiaphragm. Ultrasound and fluoroscopy identified normal diaphragmatic motion in all other patients. Thus there was complete concordance between the two techniques for diagnosis of diaphragmatic palsy.

Figure 2 Coronal view of the right hemidiaphragm (arrowheads). Liver is to the left and right lung (RL) to the right. Arrow at top left points towards the head.



Discussion

Ultrasound assessment of diaphragmatic motion has been reported previously. Haber and coworkers studied 110 adults with intra-abdominal abnormalities and commented on the usefulness of ultrasound in visualising diaphragmatic motion.[3] There have also been case reports on the use of ultrasound in children with juxtadiaphragmatic lesions,[4] eventration,[5] and paralysis of the diaphragm.[6] Harris and colleagues quantitatively studied the ventilatory movement of the right hemidiaphragm in 50 healthy adults[7] and a similar study was performed in infants.[8] Diament *et al* used ultrasound in a heterogeneous group of 14 children with suspected abnormalities of diaphragmatic motion and diagnosed paralysis of a hemidiaphragm in eight of them.[9] Watanabe and colleagues, in a large retrospective study of 125 patients with paralysed hemidiaphragm, reported that ultrasound was the only technique used to establish the diagnosis in 14 cases and ultrasound combined with fluoroscopy was used in a further 10 cases.[1] Nevertheless, fluoroscopy has remained the investigation of choice in the assessment of suspected diaphragmatic palsy in most units.

Diagnosis of diaphragmatic palsy may be delayed by reluctance to undertake a procedure that requires a child on ventilatory and inotropic support to be moved from the intensive care unit to the fluoroscopy room. Furthermore, fluoroscopy delivers an appreciable dose of radiation. In contrast, ultrasound equipment is available in all units that regularly perform cardiac surgery and it can be easily brought to the patient's bedside. Ultrasound is not known to have any dangerous side effects. Prompt diagnosis of diaphragmatic palsy is important because in some patients early plication of the affected hemidiaphragm can significantly reduce morbidity.[2]

Both techniques rely on the patient's capacity to breathe and therefore they cannot be applied to patients on full ventilatory support. Studies of phrenic nerve conduction[10] are likely to be the only method of diagnosis in this group but not many people are skilled in this technique. Also, to be of any advantage, such studies would have to be used routinely after operation because phrenic nerve palsy is not

P 25,744

Table 2 Details of patients with confirmed diaphragmatic palsy

Patient No	Age	Diagnosis	Operation	Result	Outcome
1	15 months	Fallot	Repair	L Palsy	—
2	3 years	Fallot, LMBT, WS	Repair	L Palsy	Plication
3	8 months	DS, AVSD	PAB	L Palsy	Plication
4	16 months	Fallot	Repair	L Palsy	Plication
5	22 months	Fallot, DA	Repair	L Palsy	—

L, left hemidiaphragm; LMBT, previous left modified Blalock-Taussig shunt; WS, previous Waterston shunt; DS, Down syndrome; AVSD, atrioventricular septal defect; PAB, pulmonary artery banding; DA, ductus arteriosus.

usually suspected until there is difficulty weaning a patient off artificial ventilation.

We found that ultrasound examination at the bedside was as effective as fluoroscopy in the diagnosis of a paralysed hemidiaphragm. Bedside examination facilitates early diagnosis and is of particular benefit in infants, when plication is often necessary to achieve extubation. There were no cases of paralysed right hemidiaphragm in our group, but we would not expect the diagnosis to be difficult with ultrasound because it is generally easier to image the right hemidiaphragm than the left. Bilateral palsy can be missed on fluoroscopic examination unless careful attention is given to the phases of respiration, because the two sides move in concert—albeit paradoxically. This error is less likely with ultrasound assessment because each hemidiaphragm is imaged independently. Ultrasound imaging of the left hemidiaphragm can be difficult in bigger children and adults, but diaphragmatic palsy is hardly ever the cause of major respiratory morbidity in this group and they rarely require plication.

We thank Dr Ian James, Dr Edward Sumner, and Dr Duncan Macrae of the Cardiac Intensive Care Unit for allowing us to study patients under their care.

1 Watanabe T, Trusler GA, Williams WG, Edmonds JF, Coles JG, Hosokawa Y. Phrenic nerve paralysis after paediatric cardiac surgery. Retrospective study of 125 cases. *J Thorac Cardiovasc Surg* 1987;**94**:383–8.

2 Affatato A, Villagra F, De Leon JP, *et al*. Phrenic nerve paralysis following paediatric cardiac surgery. Role of diaphragmatic plication. *J Cardiovasc Surg* 1988;**29**: 606–9.

3 Haber K, Asher WM, Freimanis AK. Echographic evaluation of diaphragmatic motion in intra-abdominal diseases. *Radiology* 1975;**114**:141–4.

4 Kangarloo H, Sukov R, Sample WF, Lipson M, Smith L. Ultrasonographic evaluation of juxtadiaphragmatic masses in children. *Radiology* 1977;**125**:785–7.

5 Haller JO, Schneider M, Kassner EG, Friedman AP, Waldroup LD. Sonographic evaluation of the chest in infants and children. *Am J Radiol* 1980;**134**:1019–27.

6 Aldrich TK, Herman JH, Rochester DF. Bilateral diaphragmatic paralysis in the new born infant. *J Pediatr* 1980; **97**:988–90.

7 Harris RS, Giovannetti M, Kim BK. Normal ventilatory movement of the right hemidiaphragm studied by ultrasonography and pneumotachography. *Radiology* 1983; **146**:141–4.

8 Laing IA, Teele RL, Stark AR. Diaphragmatic movement in newborn infants. *J Pediatr* 1988;**112**:638–43.

9 Diament MJ, Boechat MI, Kangarloo H. Real-time sector ultrasound in the evaluation of suspected abnormalities of diaphragmatic motion. *J Clin Ultrasound* 1985;**13**:539–43.

10 Mok Q, Ross-Russell R, Shinebourne EA. Prospective study of the frequency of phrenic nerve paralysis after cardiac surgery in children [Abstract]. *Br Heart J* 1989;**61**:99.

VIEWS FROM THE PAST *Ernest Henry Starling*

Starling had already published his law of the heart (see page 4) before his military service during the first world war. Using cardiac catheterisation, John McMichael, Peter Sharpey-Schafer, and Sheila Howarth questioned the general applicability of this law in studies started during the second world war (Lewis collection).

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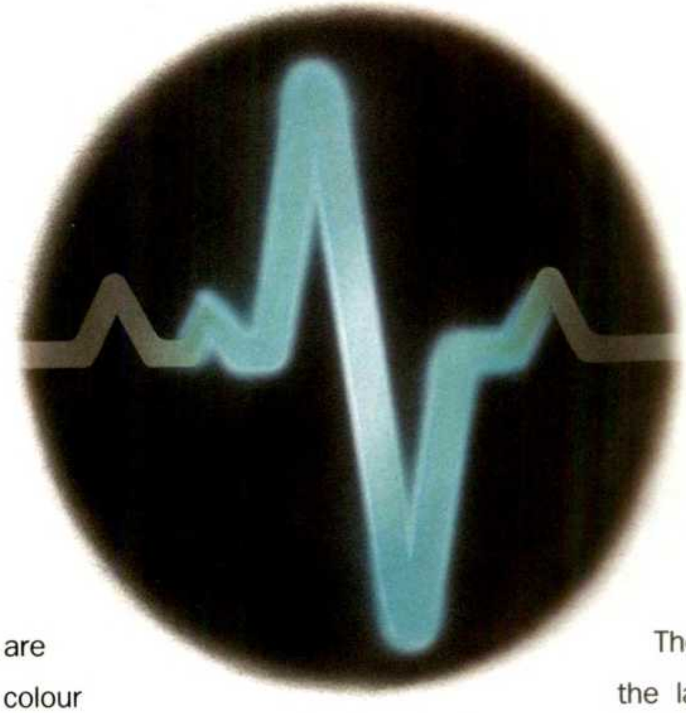

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Br Heart J 1990,64.23–4

CASE REPORT

Acute myocardial infarction caused by intravenous amphetamine abuse

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Abstract

A man aged 27 years presented with an acute myocardial infarction after injecting himself intravenously with amphetamine. Soon after admission ventricular fibrillation developed. This was successfully cardioverted. Coronary arteriography was normal.

Myocardial infarction is a rarely reported complication of amphetamine abuse. We describe a patient in whom an acute myocardial infarction developed after intravenous injection of amphetamine.

Case report

A 27 year old man injected himself intravenously with two doses (total 1·5 g) of amphetamine at an interval of half an hour. An hour later he felt unwell and after four hours severe central chest pain developed. He had previously taken amphetamine without symptoms and had misused other drugs such as heroin and cannabis. He smoked 15 cigarettes per day and drank alcohol occasionally. His father had a history of ischaemic heart disease.

Two and a half hours after the onset of chest pain he was admitted to hospital. The electrocardiogram showed evidence of an anterolateral myocardial infarction (figure). The chest radiograph was normal. He was treated with intravenous diamorphine 5 mg and prochlorperazine 12 5 mg. Soon afterwards he had a cardiac arrest and the cardiac monitor showed ventricular fibrillation. He was successfully cardioverted by a single direct current shock of 400 J. He was subsequently given 1·5 megaunits of streptokinase. Over the ensuing 24 hours the electrocardiographic monitor showed frequent ventricular extrasystoles, several self-terminating runs of ventricular tachycardia, and intermittently a nodal rhythm. Thereafter he made an uncomplicated recovery Blood taken after he was resuscitated showed a rise in serum alanine aminotransferase reaching a maximum of 224 U/l the day after admission, and in lactate dehydrogenase reaching a maximum of 556 U/l two days after admission. Gamma glutamyl transferase rose to 104 U/l two days after admission. Antibodies to hepatitis B antigen and human immunodeficiency virus were not detected in his serum. Before discharge from hospital he was able to complete a limited treadmill exercise test without symptoms developing· inverted T waves, which were evident on the electrocardiogram before exercise, became upright during exercise. He was discharged after one week and advised to take aspirin 150 mg daily. He was strongly urged to avoid drug misuse in the future.

After two months he was readmitted for additional investigations. His electrocardiogram had by now reverted to normal. Fasting blood lipids were normal. He performed a

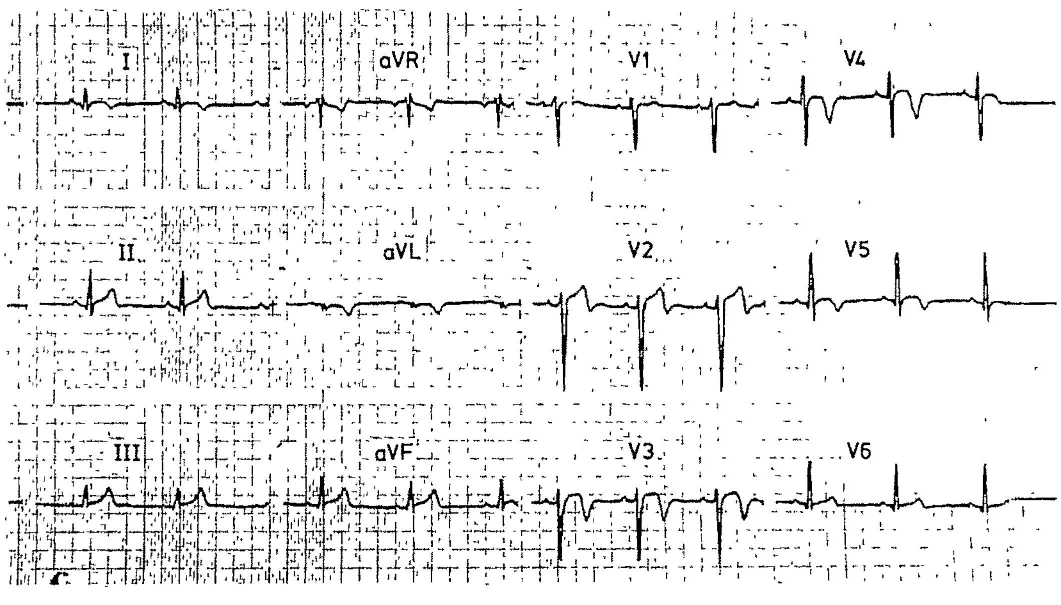

Figure Electrocardiogram on admission to hospital.

repeat exercise test using the full Bruce protocol and was able to accomplish 12 minutes without symptoms developing; the electrocardiogram remained normal throughout the test. Coronary arteriography was normal but the ventriculogram showed a small area of apical dyskinesia.

Discussion

Our patient sustained an acute myocardial infarction after intravenous injection of amphetamine. There have been only two previous reports showing a clear relation between amphetamine misuse and myocardial infarction. Carson *et al* described a patient aged 33 years in whom chest pain developed one hour after intravenous injection of amphetamine.[1] His electrocardiogram showed an inferolateral myocardial infarction; coronary arteriography was normal.[1] In the patient described by Marsden and Sheldon an anterior myocardial infarction developed after he had ingested the contents of a propylhexedrine aerosol inhaler; adult respiratory distress syndrome also developed.[2] Four of six patients reported by Anderson and Scott experienced chest pain after receiving amphetamine.[3] In one heart block also developed but the electrocardiographic findings in the other patients were not described.

Myocardial infarction after amphetamine abuse may have been caused by coronary artery spasm. Amphetamine stimulates release of noradrenaline from sympathetic nerves; this has a pressor effect on the coronary circulation.[4] Alternatively, transient occlusion of the coronary vessels may have been caused by platelet thrombi: catecholamines are known to induce platelet aggregation.[5] These effects may have been aggravated by an increase in myocardial oxygen demand induced by catecholamines.[4]

In addition to myocardial infarction, amphetamine abuse has been implicated in the aetiology of other cardiovascular disorders including acute[6] and chronic cardiomyopathy,[7] cor pulmonale,[8] necrotising vasculitis,[9] and intracranial haemorrhage.[10] It has also been implicated in the pathogenesis of congenital heart disease.[11]

There are numerous reports of death in individuals who have misused amphetamines. This was attributed to the direct effects of amphetamines—cardiac failure, cerebrovascular haemorrhage, or hyperpyrexia—or to the complications of intravenous drug abuse such as septicaemia.[10] Necropsy studies on the heart in patients who died suddenly after amphetamine misuse showed either no abnormality[10] or various changes including myocardial congestion,[12] arteriolar spasm,[13] rupture of myocardial fibres,[14] and small interstitial[14] and endocardial haemorrhages[15]; there are no reports of myocardial infarction. Although amphetamine abuse has the potential to cause myocardial infarction, it is likely that in many cases ventricular fibrillation supervenes before the changes of myocardial infarction become manifest.

Cocaine abuse has been strongly associated with myocardial infarction.[16 17] Like amphetamine, it enhances noradrenaline release and probably causes myocardial ischaemia by inducing coronary artery vasospasm and by increasing myocardial oxygen demand.[16 17] Recreational use of the purer, free-base form of cocaine (crack) has reached epidemic proportions in North America and there are fears that use of crack could become widespread in the United Kingdom.[18] Cocaine is often diluted (cut) with other agents such as amphetamine before it is sold, so drug misusers are often unaware of the exact composition of the drugs they are taking.[19] This raises the possibility that the patient we describe may inadvertently have taken a combination of amphetamine and cocaine which may have had an additive effect in provoking myocardial ischaemia.

1 Carson P, Oldroyd K, Phadke K Myocardial infarction due to amphetamine *Br Med J* 1987;294:1525–6.
2 Marsden P, Sheldon J. Acute poisoning by propylhexedrine. *Br Med J* 1972;i:730
3 Anderson EW, Scott WC Cardiovascular effects of benzedrine *Lancet* 1936;ii:1461–2.
4 Feigl EO Coronary physiology *Physiol Rev* 1983;63:1–205
5 Haft JI, Kranz PD, Albert FJ, Fanoi K Intravascular platelet aggregation in the heart induced by norepinephrine microscopic studies *Circulation* 1972,46:698–708.
6 Call TD, Hartneck J, Dickinson WA, Hartman CW, Bartel AG Acute cardiomyopathy secondary to intravenous amphetamine abuse *Ann Intern Med* 1982;97:559–60.
7 Croft CH, Firth BG, Hillis LD Propylhexedrine-induced left ventricular dysfunction *Ann Intern Med* 1982; 97·560–1.
8 Anderson RJ, Garza HR, Garriot JC, Dimaio V. Intravenous propylhexedrine (Benzedrex) abuse and sudden death. *Am J Med* 1979;67:15–20
9 Citron BP, Halpern M, McCarron M Necrotizing angiitis associated with drug abuse *N Engl J Med* 1970;283: 1003–11
10 Kalant H, Kalant OJ Death in amphetamine users causes and rates *Can Med Assoc J* 1975;112 299–304.
11 Nora JJ, Vargo TA, Nora AH, Love KE, McNamara DG. Dexamphetamine: a possible environmental trigger in cardiovascular malformations. *Lancet* 1970,i:1290–1.
12 Cravey RH, Reed D Intravenous amphetamine poisoning. Report of three cases. *J Forensic Sci Soc* 1970,10:109–12.
13 Richards HGH, Stephens A Sudden death associated with the taking of amphetamines by an asthmatic. *Med Sci Law* 1973,1·35–8
14 Fukunaga T, Mizoi Y, Adachi J, Tatsumo Y. Metamphetamine concentrations in blood, urine, and organs of fatal cases after abuse. *Jpn J Legal Med* 1987,41 328–34.
15 Orrenius S, Maehly AC Lethal amphetamine intoxication A report of three cases *J Legal Med* 1970,67 184–9
16 Smith HWB, Liberman HA, Brody SL, Battey LL, Donohue BC, Morris DC Acute myocardial infarction temporarily related to cocaine use. *Ann Intern Med* 1987,107:13–8.
17 Cregler LL, Mark H. Medical complications of cocaine abuse. *N Engl J Med* 1986,315:1495–500.
18 Kleber HD. Epidemic cocaine abuse: America's present, Britain's future? *Br J Addict* 1988,83:1359–71
19 Oldroyd K, Phadke K, Carson P. Complications of cocaine abuse *Ann Intern Med* 1987,107.940.

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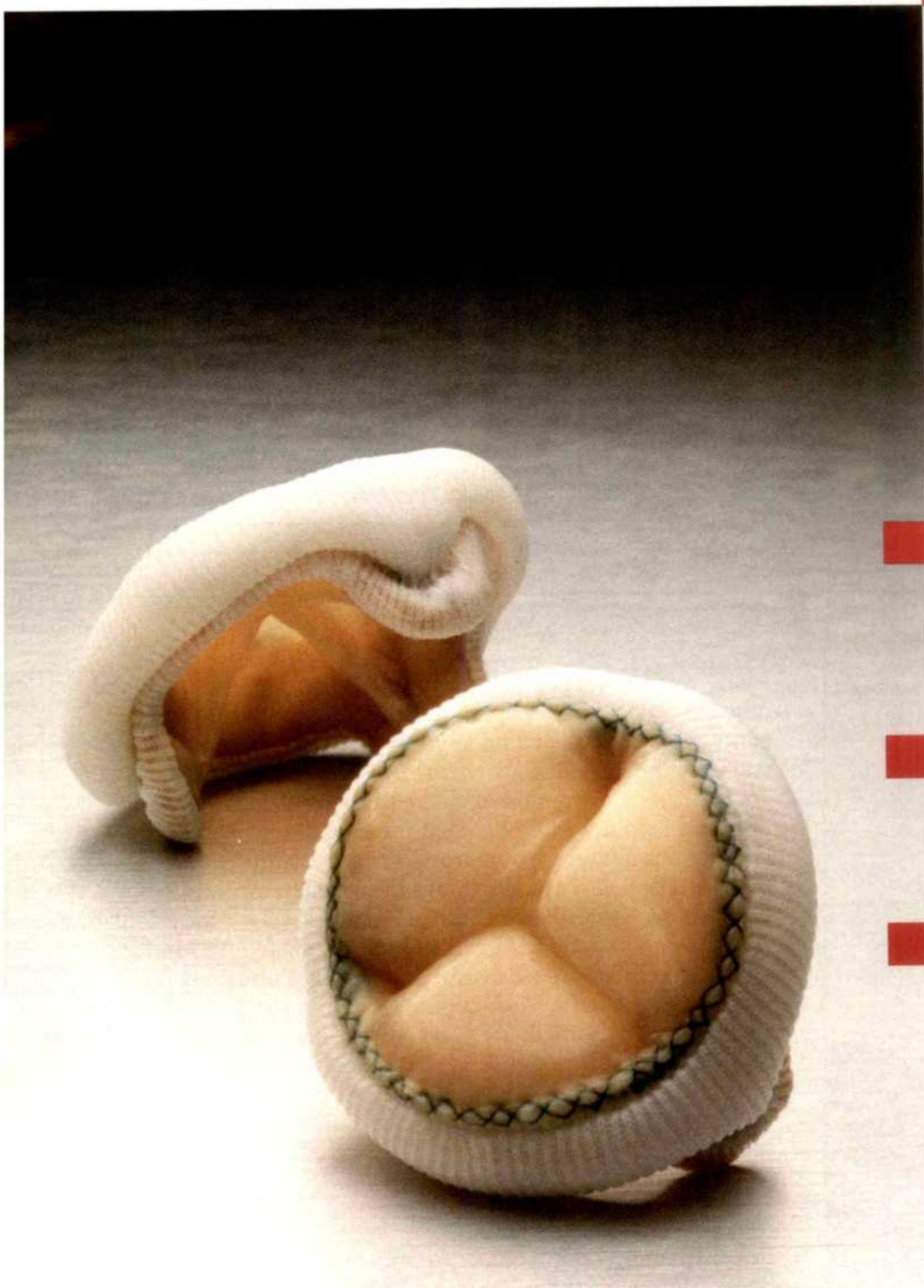

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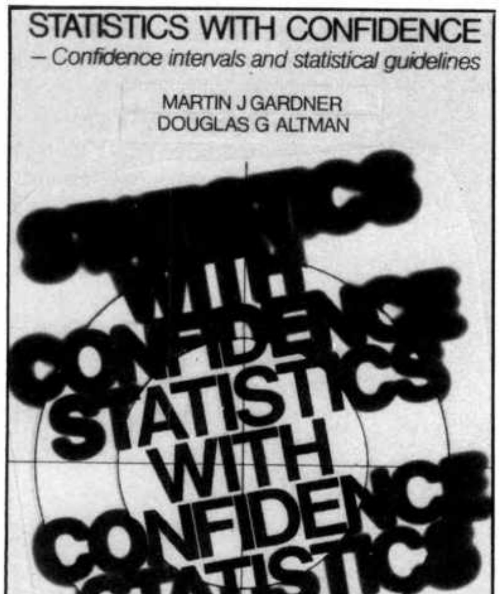
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Br Heart J 1990,64·25–31

TECHNOLOGY

Comparison of the normal sinus node with seven types of rate responsive pacemaker during everyday activity

A N Sulke, A Pipilis, R A Henderson, C A Bucknall, E Sowton

Abstract

The heart rate response of 59 patients aged 17–79 years implanted with seven different types of rate responsive pacemakers was evaluated during graded exercise treadmill testing and during standardised daily activities. The heart rate response in patients with pacemakers was compared with the chronotropic response in 20 healthy controls of similar age and sex distribution who performed identical protocols. All pacemaker types adequately simulated the control heart rate response during the graded exercise treadmill test except during the early stages of exercise. However, during everyday activities, the response of ventricular rate responsive (VVIR) pacemakers was varied. Activity sensing systems rapidly overresponded to staircase descent, to changes in walking speed, and to suitcase lifting with the pacemaker arm, and these systems did not respond to mental stress. "Physiological" sensors (QT and minute ventilation units) responded slowly to rapid changes in physiological demand. The QT pacemaker patients did respond to mental stress but showed a paradoxical increase in rate during the recovery phases of burst exercise protocols such as staircase ascent/descent and walking deceleration. Dual chamber pacemakers in VDD, DDD, and DDDR modes most closely simulated the normal chronotropic response during everyday activities.

Graded exercise treadmill testing, in isolation, may not be the best way to assess or program the heart rate response in patients with rate adaptive pacemakers because changes in heart rate during everyday activities may deviate considerably from the normal sinus response despite satisfactory simulation of the normal chronotropic response during treadmill testing.

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12 February 1990

Pacemaker implantation, as well as increasing life expectancy by preventing Adams-Stokes seizures and life threatening bradycardias,[1] can also improve the patient's quality of life by increasing physical capability.[2] Rate responsive pacing systems are now increasingly used to achieve this end.

The advantages of single chamber rate responsive pacing over VVI pacing are now well established.[3–7] Several different types of rate responsive pacemakers are currently available (both single and dual chamber) with various sensors including those that detect activity,[8] minute ventilation,[9] QT interval,[10] central venous temperature,[11] venous oxygen saturation,[12] pH value,[13] and, more recently, dP/dt[14] and the integral of the evoked response.[15]

Most previous studies to assess sensor driven rate responsive pacemakers used treadmill testing or bicycle ergometry.[16–18] We compared heart rate changes in patients with single and dual chamber rate responsive pacemakers with the chronotropic response in a group of healthy controls during various standardised everyday activities and during graded exercise treadmill tests.

Patients and methods

PATIENTS

Fifty nine patients aged 17–79 years (mean 57·9, 35 (59%) men) had seven types of rate responsive pacemaker implanted. Ventricular rate responsive pacemakers (VVIR) were implanted in 33 patients. They were the activity sensing Siemens Sensolog I (10), minute ventilation sensing Telectronics Meta (8), activity sensing Medtronic Activitrax (8), and QT sensing Vitatron Tx II (7). None of these patients had the signs or symptoms of the pacemaker syndrome.[19]

Dual chamber rate responsive systems were implanted in 26 patients. Six had Medico Phymos VDD systems, which require a single lead with free floating atrial bipolar sensing and unipolar ventricular sensing and pacing; 10 had DDD systems; and 10 had activity sensing DDDR systems. The table shows the indications for implantation.

All patients were followed up at 6 weeks and 3 months after pacemaker implantation and were optimally programmed to the rate response mode according to the manufacturers' instructions.

We studied heart rate responses in a group of 20 apparently healthy people aged 23–76 years (mean 55·0, 12 (60%) men) during standardised daily activities and treadmill testing.

Patient details and indication for pacemaker implantation

Pacemaker type	*Mode*	*No*	*No male (%)*	*Age range (mean)*	*Indication for implant*
Telectronic Meta	VVIR	8	2 (25)	38–79 (63·3)	PHA(2),B(2),AVII+AVIII(4)
Medtronic Activitrax	VVIR	8	1 (12·5)	22–77 (58·9)	PHA(3),AF+B(1),SSS(2),AVII+AVIII(2)
Siemens Sensolog	VVIR	10	8 (80)	43–73 (55·8)	PHA(5),AF+B(1),SSS(1),B(1),AVII+AVIII(2)
Vitatron Tx II	VVIR	7	5 (71)	52–69 (57·9)	PHA(2),AF+B(2),SSS(2),AVII+AVIII(1)
Medico Phymos	VDD	6	5 (83)	52–78 (62·1)	AVII(2),AVIII(4)
Various	DDD	10	8 (80)	22–77 (59·6)	B(1),SSS+AVII(1),AVII(2),AVII+AVIII(6)
Siemens Multilog (3) Pacesetter Synchrony (7)	DDDR	10	6 (60)	17–68 (50·6)	SSS+AVII+AVIII(8),AVII+AVIII(2)
Total		59	35 (59)	17–79 (57·9)	

PHA, post His bundle ablation; B, symptomatic bradycardia; AF, slow atrial fibrillation; SSS, sick sinus syndrome, AVII, 2nd degree atrioventricular block (Mobitz type II); AVIII, complete atrioventricular block.

HEART RATE MONITORING

During the study continuous six lead electrocardiograms were recorded with a Siemens Mingolog 7 at a paper speed of 25 mm/s. The heart rate was calculated from the mean RR interval of the five consecutive beats recorded immediately after each stage was completed. Before each activity protocol the resting heart rate was measured after the individual had sat at rest for 2 minutes.

STUDY PROTOCOLS: GRADED TREADMILL TEST

Patients performed graded exercise treadmill testing according to the Chronotropic Assessment Exercise Protocol (CAEP).[20] All individuals were exercised to peak effort tolerance.

POSTURE CHANGE

The effects of changes in posture on heart rate were determined by measuring mean RR interval over five beats when the individual was lying, seated, and standing. Heart rate was measured after individuals had rested supine on a standard examination couch for 2 minutes. The heart rate was measured immediately after the subjects sat upright and immediately they stood up.

MENTAL STRESS

The effect of mental stress on heart rate was determined over a 2 minute period during which the individual was asked to subtract 7 from 100 serially aloud. The supervising clinician vigorously encouraged the subject throughout the study period. Heart rate was measured at rest before mental stress, after 60 seconds of stress, and after 120 seconds of stress (that is, immediately after it stopped.

SUITCASE LIFTING

The subjects were asked to lift a standard suitcase (45 cm × 35 cm × 12 cm weighing 10 kg) with both hands from the floor on to the examination couch (a height of 82 cm) and then immediately back on to the floor. Heart rate was measured before and immediately after they lifted the suitcase.

Subjects were then randomly assigned to suitcase lifting with either the right or left arm and instructed to raise the case from the floor to above hip height four times without stopping and heart rate was assessed at rest and after the procedure. The subject was rested until the basal heart rate was achieved and they repeated the suitcase lifts with the opposite arm.

CHANGES IN WALKING SPEED

We assessed the response of heart rate to rapid acceleration and deceleration and talking while walking.

Subjects were rested until basal heart rate was attained (stage 0). They were then instructed to walk with normal arm movement on a treadmill at 1 mph (1·6 km/h) and 0° gradient for 30 seconds (stage 1). They were then engaged in active conversation (discussing their travel plans to and from the study centre) while walking normally at this treadmill rate for 30 seconds (stage 2). Treadmill speed was gradually accelerated over the next 30 seconds to reach 4 mph (6·4 km/h) (stage 3). This rate was maintained for a further 30 seconds (stage 4). The treadmill rate was then gradually decelerated to 1 mph (1·6 km/h) during the next 30 seconds (stage 5). The treadmill was maintained at 1 mph (1·6 km/h) for the final 30 seconds of the procedure (stage 6). Throughout, individuals were encouraged to walk without using the support bars, if possible.

STAIRCASE ASCENT AND DESCENT

We measured the response of heart rate to staircase ascent and descent from telemetered electrocardiographic recordings from a Hewlett Packard 78571B recorder.

Subjects were asked to climb two flights of stairs (30 steps, each 15 cm tall, pitch 27 cm) as rapidly as possible and to rest in the erect posture at the top of the second flight. Heart rate was measured at rest and every 15 seconds from the start of the ascent.

Once heart rate had returned to resting values individuals were asked to descend the stairs as fast as possible and to rest at the base of the second flight. Heart rate during staircase descent was calculated every 15 seconds from start of the descent.

STATISTICAL ANALYSIS

Heart rate and percentage change in heart rate were calculated for each individual at every stage of the protocol in the study, where percentage change in heart rate = observed heart rate − resting heart rate ÷ resting heart rate × 100

Mean heart rate and mean percentage change in heart rate were calculated for each pacemaker type and for the control population for every stage of each protocol.

We used unpaired Student's t tests to measure statistical differences between percentage change in heart rates in the pacemaker

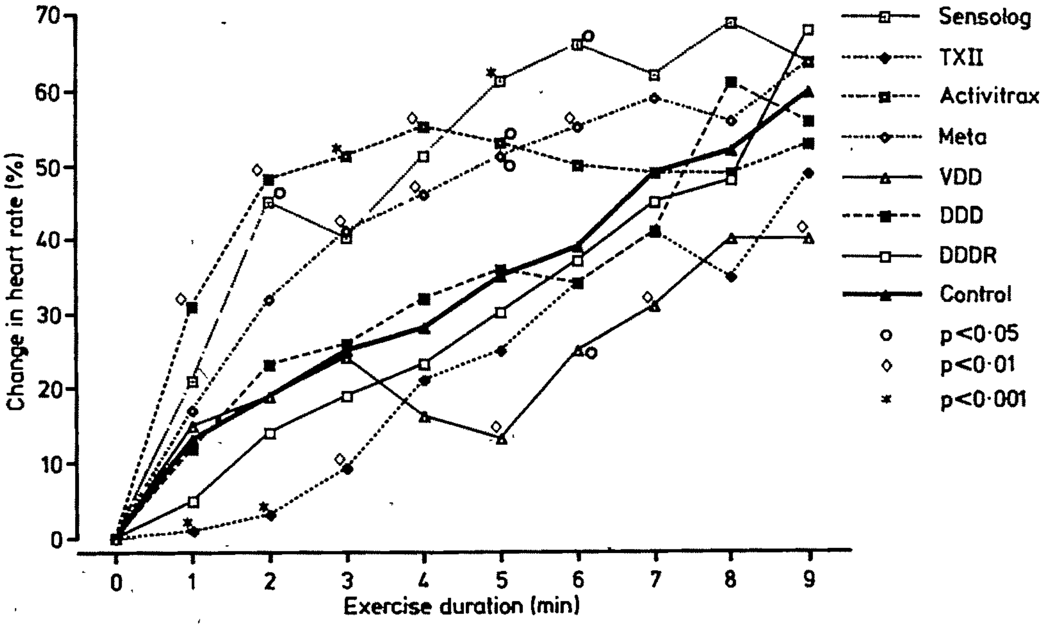


Figure 1 A comparison by the graded exercise treadmill test of seven different types of rate responsive pacemaker.

groups and the controls. A p value of <0·05 was regarded as statistically significant.

Results

GRADED EXERCISE TREADMILL TESTS (FIG 1)

During the first 4 minutes of exercise the observed increase in heart rate varied in all single chamber systems. Sensolog, Activitrax, and Meta significantly overresponded while Vitatron Tx patients were significantly ($p < 0.001$) underresponsive compared with the value in the controls.

During the latter stages of the exercise test and the recovery phase all pacemakers closely simulated heart rate changes in the controls. During recovery, heart rate fell appropriately in all groups except for Vitatron Tx patients in whom high rates decayed more slowly ($p < 0.05$) than in the controls. The VDD patients showed a significant ($p < 0.01$) underresponse after 5 minutes of exercise because the essential rate limiting programming required a pacemaker Wenckebach 2:3 block to start at comparatively low heart rates unless a very short (< 100 ms) atrioventricular delay was programmed. This trend occurred in both the other dual chamber modes at high workloads but did not reach statistical significance.

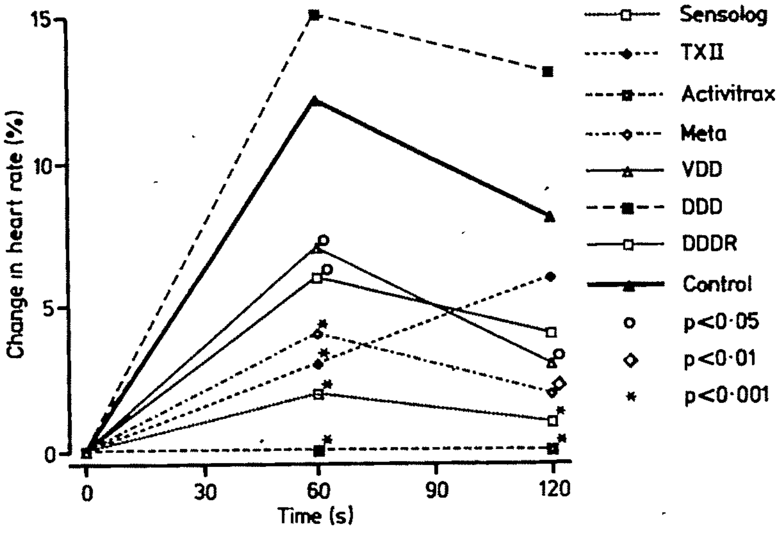


Figure 2 The effect of mental stress on change in heart rate in controls and patients with pacemakers.

POSTURE CHANGE

In the controls the heart rate increased when they sat up from the lying position, and increased further when they stood up from the sitting position. The heart rate response with dual chamber and Sensolog pacemakers was similar to that of the controls.

The heart rate response to posture change in patients with Activitrax, Meta, and Vitatron Tx pacemakers was significantly less than that in the controls ($p < 0.05$, $p < 0.001$, and $p < 0.001$ respectively).

MENTAL STRESS (FIG 2)

The increase in heart rate seen during mental stress was similar in patients with DDD pacemakers and controls. Initially the heart rate response in patients with VDD and DDDR pacemakers was significantly less than that in the controls ($p < 0.05$), though at the end of the mental stress test the heart rate response was similar to that of the controls. The Vitatron Tx group showed a delayed heart rate response to mental stress but the mean percentage increase at the end of the stress protocol was similar to that of the controls. Patients with all other pacemakers showed little or no response to mental stress and the changes in heart rate in these patients were significantly less than those in the controls ($p < 0.001$).

SUITCASE LIFTING (FIG 3)

The increase in heart rate in the controls was similar with four lifts of the right or left arm or a single lift with both arms. All pacemakers performed well except the Vitatron Tx which significantly underresponded ($p < 0.01$) to all forms of suitcase lifting. Patients with Sensolog

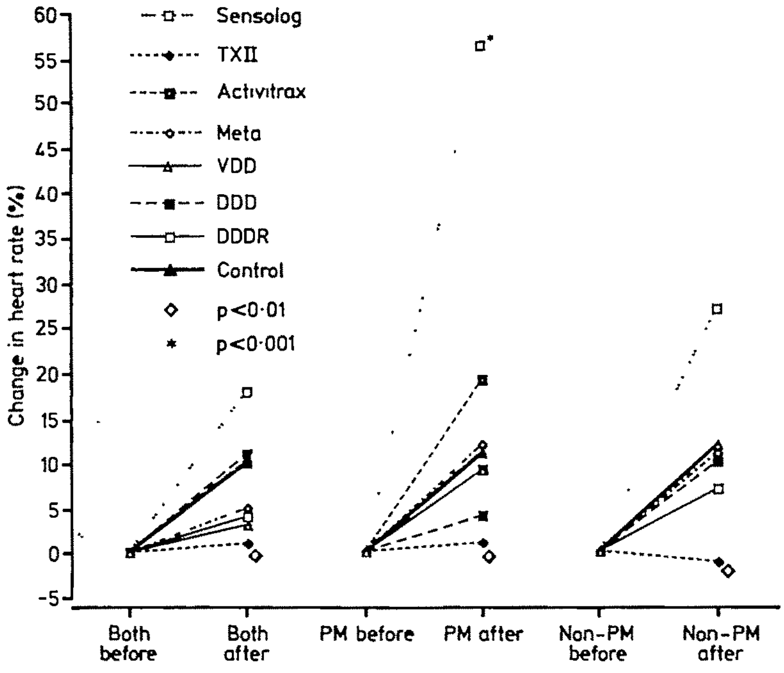


Figure 3 The effect of suitcase lifting on heart rate in controls and patients with pacemakers. Both before, before lifting with both arms; both after, after lifting with both arms; PM before, before lifting with pacemaker arm, PM after, after lifting with pacemaker arm; non-PM before, before lifting with non-pacemaker arm; non-PM after, after lifting with non-pacemaker arm.

pacemakers significantly overresponded to suitcase lifting with the pacemaker arm ($p < 0{\cdot}001$), and patients with Activitrax pacemakers showed a similar trend ($p < 0{\cdot}08$).

CHANGE IN WALKING SPEED (FIG 4)

The controls showed a gradual increase in heart rate with a greater increase after stage 4 and a gradual decrease in heart rate after stage 5. Dual chamber systems closely mimicked the normal sinus response at all stages of this protocol.

Vitatron Tx patients responded slowly to the acceleration phase (stage 3) and fast walking (stage 4) with a paradoxical rate increase during the deceleration phase (stage 5) and final slow walking (stage 6).

The activity sensing VVIR systems produced greater increases in heart rate than were seen in controls ($p < 0{\cdot}001$) at all stages.

Meta patients overresponded to the acceleration, fast walking, deceleration, and final slow walk (stages 3–6) but the increase in heart rate was appropriate during slow walking and talking.

STAIRCASE ASCENT (FIG 5)

All individuals completed the ascent within 15 seconds and therefore the remaining 60 seconds of the protocol represents the recovery period. Controls showed a rapid increase in heart rate to a peak after 15 seconds of the protocol, with a plateau at 30 seconds and a gradual decay to resting rate by 75 seconds. Both Meta patients ($p < 0{\cdot}01$) and Vitatron Tx patients ($p < 0{\cdot}001$) underresponded to the initial effort of rapid staircase ascent. Vitatron Tx patients also showed a paradoxical rate increase up to 45 seconds after the initial exertion.

During ascent and recovery, patients with the Activitrax, VDD, DDD, and DDDR systems and controls had similar changes in heart rate.

STAIRCASE DESCENT

Controls showed half the change in heart rate seen in staircase ascent with a gradual decrease in heart rate from 15 seconds to resting rate by 60 seconds. Activity sensing pacemakers (Sensolog, Activitrax, and DDDR) initially overresponded to rapid staircase descent ($p < 0{\cdot}001$, $p < 0{\cdot}01$, and $p < 0{\cdot}05$ respectively). Sensolog patients were slow to return to resting heart rate after the initial exertion.

Vitatron Tx patients underresponded to the

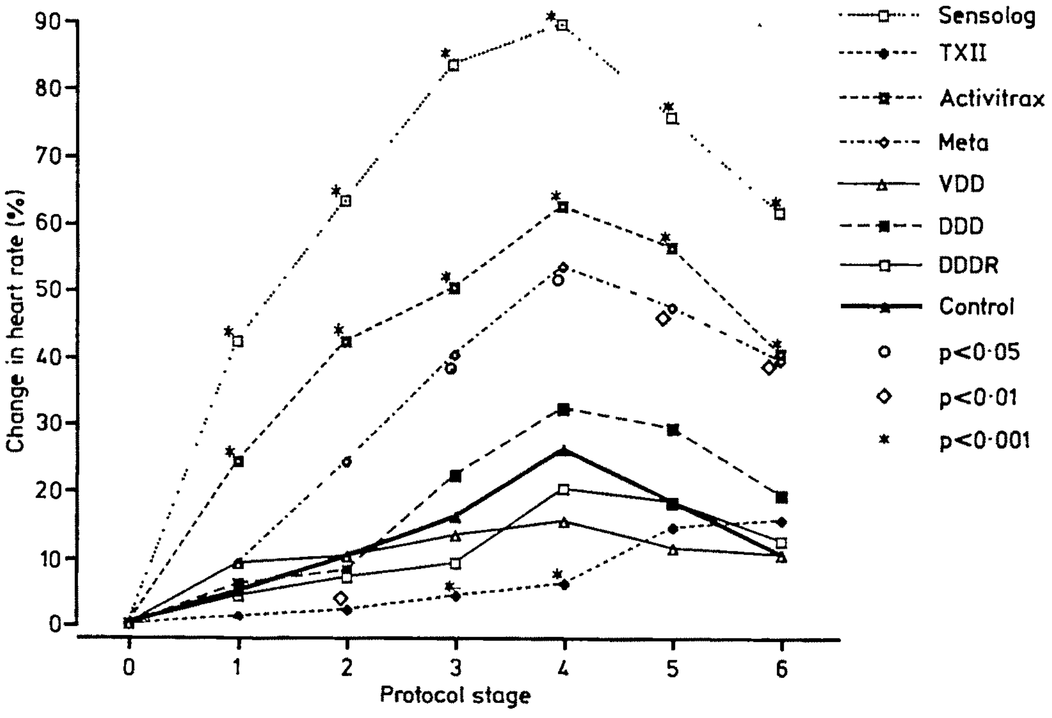
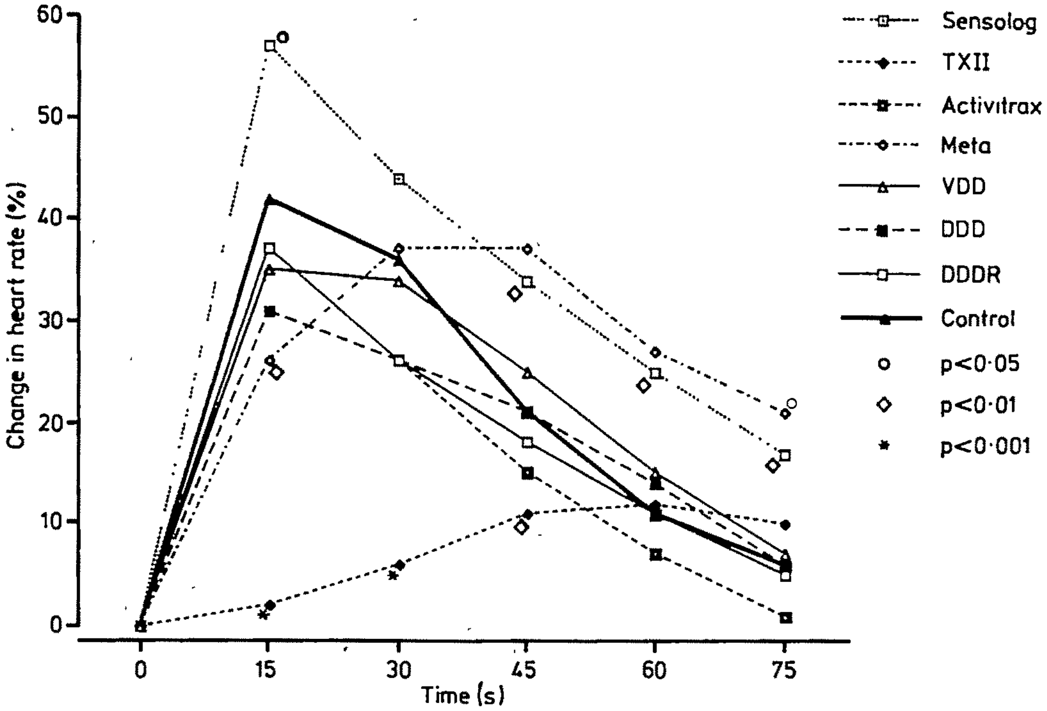


Figure 4 Effect of walking acceleration and deceleration on change in heart rate. Protocol stages are described in text.

Figure 5 The effect of ascending stairs on change in heart rate.



initial effort phase ($p < 0.001$) and showed a paradoxical rate increase in the recovery phase. Patients with Meta and DDD systems showed no significant difference in changes in heart rate compared with the controls.

Discussion

Previous studies comparing adaptive rate pacing and fixed rate pacing[21–23] and those comparing different types of rate responsive pacemakers[16–18] used either treadmill testing or bicycle ergometry to assess haemodynamic function, oxygen consumption, and the heart rate response. In addition, the graded exercise treadmill test is widely used to assess the programming of rate responsive systems.[24]

However, burst exercise is far more common in everyday out of hospital activity than gradually increasing or prolonged physical exertion. Treadmill exercise is also "synthetic" in that the normal movement of the upper body is largely inhibited by both bicycle ergometry and exercise treadmill testing because patients grip either cycle handlebars or treadmill support bars.

We compared the heart rate response of patients with seven different types of rate responsive pacemakers, both dual and single chamber, with the natural chronotropic response of the normal sinus node during various standardised daily activities and during a graded exercise treadmill test. The study was designed to reproduce commonly encountered daily activities that involve burst exercise and also mental stress at rest.

In our patients the paced heart rate response during the graded exercise treadmill tests closely simulated the heart rate response in apparently healthy controls. This is not surprising because rate adaptive pacemakers are developed and evaluated by such tests. These findings confirm those of previous comparative studies,[16–18] and also suggest that by conventional criteria programming of the pacemakers under study was appropriate.[25]

During the early exercise phase (up to stage 2, or 4 minutes of exercise) the single chamber units that sensed activity and minute ventilation overresponded while the QT sensing pacemakers underresponded. Dual chamber pacemakers most closely simulated the natural chronotropic response. During the later exercise stages, however, the single chamber units more accurately simulated the normal response. In the dual chamber systems rate limiting programming, which avoids a pacemaker mediated "endless loop" tachycardia by inducing Wenckebach or 2:1 block, caused underresponse at high metabolic demand. These data confirm previous studies of the performance of the single chamber units during treadmill testing.[8–10]

Assessment by the treadmill test indicates that the pacemakers under study are adequate simulators of the normal chronotropic response. The performance of the single chamber units assessed by the daily activity protocols was, however, less satisfactory. During posture change, control heart rates increased more during the change from lying to sitting than from sitting to standing. This was probably because the height of the examination couch meant that subjects required less effort to "stand down" from the seated posture than to rise from the supine to the seated position. The dual chamber systems and the activity sensing Sensolog VVIR pacemakers responded appropriately to this protocol.

The activity sensing units (Sensolog and Activitrax) tended to rapidly overrespond to most of the burst exercise protocols. These were specifically designed to evaluate pacemaker response while subjects were uninhibited by support bars and therefore showed the same movement of the upper body that would be encountered during everyday living. The almost universal overresponse suggests that algorithms were designed on the basis of response during "synthetic" exercise such as treadmill exercise or bicycle ergometry. When the patient has uninhibited physical mobility the manufacturers' suggestions for the settings of slope and threshold produce a relative overresponse of paced heart rate for a given physiological demand. There was no significant response to mental, resting stress as would be expected from the sensitivity and specificity of this type of sensor that is described as "non-physiological" by Rossi.[26] Similarly, lack of heart rate response to the Valsalva manoeuvre and hand grip was shown with activity sensors.[27] Both Activitrax and Sensolog overresponded to suitcase lifting with the pacemaker arm, but responded appropriately to lifting with both arms and to arm lifting on the non-pacemaker side, again suggesting oversensitivity to movement of the upper torso. The piezo sensor is shaken more when the pectoral muscle on the side of the implant is active than when there is counterbalancing by symmetrical activity of the upper torso as when both arms are lifted or when lifting with the opposite arm.

The variation in the response of the two types of activity sensing pacemaker, as well as being the result of differing programming recommendations by the manufacturers, may also be the result of different processing of the sensor signal. The piezo crystal, which is bonded to the can in the Sensolog unit, and the activity sensors in both DDDR units that we studied, respond more to pressure than vibration because processing takes account of amplitude, frequency, and total variation in signal length. In the Activitrax pacemaker the sensor is also can-bonded but responds more to can vibration, with the piezo crystal acting partly as a vibration counter, and less to pressure over the pacemaker itself.[28] This may make the Activitrax less specific than the Sensolog but the programming algorithms seem to allow better simulation of the natural chronotropic response to a wider variety of daily activities with the Activitrax than with the Sensolog.

The Meta unit, which senses minute ventilation, and Vitatron Tx, which senses the stimulus-QT interval, proved slow to react to burst exercise and tended to underrespond to most protocols. Similar findings were recently reported with these pacemakers during the performance of daily activities.[29] The Tx units often responded so slowly to stress—for example staircase ascent and descent and walking deceleration—that rates increased paradoxically in the recovery phases. This slowness to respond is the result of the changes in the stimulus-QT interval at the start of exercise. Baig *et al* showed an acute prolongation of the stimulus-QT interval at the start of treadmill exercise before the widely accepted shortening after more prolonged stress.[30] Despite improvements in detection algorithms and rate response slopes this finding will make it difficult for this type of sensor to respond rapidly and accurately to everyday burst activity. Patients with Vitatron Tx units, however, responded best of all the VVIR systems to the mental stress protocol, closely simulating the natural chronotropic response. This confirms that functioning of this sensor was more "physiological", with the response based on a probable increase in adrenergic drive during the protocol; this ultimately shortened the stimulus-QT interval giving a good simulation of the normal chronotropic response to resting stress.

The Meta patients underresponded to mental stress and change in posture. They were slow to respond when they walked up a staircase and remained in high rate response well into the recovery period, though their response to walking down stairs was appropriate. This sensor lacks specificity because an increase in heart rate does not always correlate with an increase in either respiratory rate or minute ventilation.[26] Thus though there was significantly more response to resting stress than that found with the activity sensors it was significantly less than in the controls. The persistence of high heart rates during recovery phases paralleled the increased respiratory rate which decays more slowly than heart rate in controls.

Other workers found a paradoxical change in pacing rate in patients implanted with Meta units when they performed the Valsalva manoeuvre while supine.[31] An increase in rate with arm swinging was also reported with VVIR units sensing minute ventilation and units sensing respiratory rate such as the Biotec Biorate[32]; we did not find that this was an important effect in our studies.

The dual chamber pacemakers all tended to simulate the natural chronotopic response during standardised daily activities. In our study the Medico Phymos VDD units underresponded to mental stress. This was because in two patients heart rate increased sufficiently to activate the rate limiting function that was programmed to avoid pacemaker mediated tachycardia by inducing a 2:3 heart block at rates over 150 beats per minute. This may have biased the group result and it is therefore difficult to draw firm conclusions from these data.

Most patients implanted with DDDR pacemakers in this study had both sinus node dysfunction and high grade atrioventricular block. This system, therefore, is the only one we have assessed where a "combination" sensor is operating by tracking the sinus response and using an activity sensor to augment the rate response and thus "support" the sinus node when its response is inadequate. During mental stress when the activity sensor is not contributing to the rate adaptation, the tracking response increases heart rate although significantly less than in controls. The activity sensor, however, seems to predominate during the staircase descent protocol, causing an initial overresponse to this stress. Overall, however, these units performed better than any of the single sensor, single chamber rate adaptive pacemakers we studied.

In all but one patient with a DDD pacemaker in our study group, the response of the sinus node to exercise was normal. Overall simulation of the normal chronotropic response during the everyday activity protocols was best in patients with DDD pacemakers.

CONCLUSION

All the pacemakers under investigation showed appropriate heart rate response to exercise treadmill testing when compared with healthy controls. Our data show that the simulation of natural chronotropic response during daily activities is generally poor in patients implanted with VVIR pacemakers. The advantages and disadvantages of different sensors depend on their specificity and sensitivity to increased physiological demand.

A combination sensor may improve the rate adaptation of single chamber rate responsive pacemakers during everyday activity. Early rate adaptation to physical stress by sensors that rapidly respond to activity followed by later input by "physiological" sensors (that is those that respond to minute ventilation, stimulus to QT interval, pH, temperature, or oxygen saturation) would improve pacemaker sensitivity and specificity to a wide variety of stresses and facilitate better simulation of the normal sinus node response to everyday activities and circadian variations in heart rate.[33] Recent work with multiple sensors seems promising.[34]

At present, dual chamber pacemakers still give the best form of rate responsive pacing in terms of heart rate changes during everyday activities.

1 Alt E, Volker R, Wirtzfeld A, Ulm K. Survival and follow-up after pacemaker implantation: a comparison of patients with sick sinus syndrome, complete heart block and atrial fibrillation. *PACE* 1985,8.849–55.

2 Rickards AF, Donaldson RM Rate responsive pacing. *Clin Prog Pacing Electrophysiol* 1983,1:12–9.

3 Karlof I. Haemodynamic effect of atrial triggered versus fixed rate pacing at rest and during exercise in complete heart block. *Acta Med Scand* 1975,197:195–203.

4 Rossi P, Rognoni G, Occhetta E, *et al* Respiration dependent ventricular pacing compared with fixed ventricular and A-V synchronous pacing· aerobic and haemodynamic variables. *J Am Coll Cardiol* 1985;6·646–52

5 Beyersdorf F, Kreuzer J, Happ J, Zegelman M, Satter P. Increase in cardiac output with rate responsive pacemakers *Ann Thorac Surg* 1986,42:201–5.

6 Humen DP, Kostuk WS, Klein GJ. Activity sensing, rate responsive pacing improvement in myocardial performance with exercise. *PACE* 1985;8 52–9

7 Lau CP, Camm AJ Role of left ventricular function and Doppler derived variables in predicting haemodynamic benefits of rate responsive pacing. *Am J Cardiol* 1988,62 906–11.

8 Humen DP, Anderson K, Brumwell D, *et al.* A pacemaker which automatically increases its rate with physical activity In *World symposium of cardiac pacing: proceedings* Dormstadt, Federal Republic of Germany. Steinkopff Verlag, 1983 259–64

9 Rossi P, Plicchi G, Canducci GC, Rognoni G, Aina F. Respiratory rate as a determinant of optimal pacing rate. *PACE* 1983,6·502–10.

10 Rickards AF, Donaldson RM, Thalen HJ The use of QT interval to determine pacing rate early clinical experience *PACE* 1983;6:346–54

11 Alt E, Hirgstetter C, Heinze M, Blomer H Rate control of physiologic pacemakers by central venous blood temperature *Circulation* 1986,73·1206–12

12 Wirtzfeld A, Goedel-Meinen L, Bock T, Heinze R, Liss HD, Munteanu J Central venous oxygen saturation for the control of automatic rate responsive pacing *PACE* 1982;5 829–35

13 Cammilli L, Alcidi L, Papeschi G, *et al* Preliminary experience with pH-triggered pacemaker. *PACE* 1978, 1.448–57

14 Sutton R, Sharma A, Ingram A, Camm J, Lindemans F, Bennett T First derivative of right ventricular pressure as a sensor for an implantable rate response VVI pacemaker [Abstract]. *PACE* 1988,11 487

15 Callaghan F, Scamerlo J, Tarjarn P The ventricular depolarisation gradient exercise performance of a closed loop rate responsive pacemaker [Abstract]. *PACE* 1987;10 1212

16 Kenny RA, Ingram A, Mitsouka T, Walsh K, Sutton R Comparison of sensor driven physiological pacing systems [Abstract] *PACE* 1985,8·781

17 Alt E, Volker R, Hogl B, MacCarter D Comparison of Activitrax and Nova MR pacemakers with VVI/AAI pacing *Circulation* 1988,78 (suppl III).116–24.

18 Maisch B, Langenfeld H. Rate adaptive pacing—clinical experience with 3 different pacing systems. *PACE* 1986,9 997–1004

19 Ausubel K, Furman S The pacemaker syndrome *Ann Intern Med* 1985,103 420–9.

20 Wilkoff BL, Corey J, Blackburn C Analytic techniques in the assessment of chronotropic response to exercise [Abstract] *PACE* 1988;11 530

21 Lipkin DP, Buller N, Frenneaux M, *et al* Randomised crossover trial of rate responsive Activitrax and conventional fixed rate ventricular pacing *Br Heart J* 1987; 58 613–6

22 Faerestrand S, Breivik K, Ohm O Assessment of the work capacity and relationship between rate response and exercise tolerance associated with activity sensing rate responsive ventricular pacing *PACE* 1987;10.1277–90

23 Nordlander R, Pehrsson SK, Astron H, Karlsson J Myocardial demands of atrial-triggered versus fixed rate ventricular pacing in patients with complete heart block. *PACE* 1987,10.1154–9

24 Sharma A, Bennett T, Sutton R, Ericson M, Yee R, Klein G. Randomised single blind assessment of rate responsive pacing based upon maximum positive right ventricular dP/dt during treadmill exercise [Abstract] *PACE* 1988,11:487.

25 Ryden L, Kristenssen B-E Rate responsive pacing effects on haemodynamics, exercise tolerance, and subjective feeling of wellbeing In· Zipes DP, Jalife J, eds *Rate responsive pacing*. New York: Grune, 1985 513–22.

26 Rossi P. Rate responsive pacing: biosensor reliability and physiological sensitivity *PACE* 1987;10.454–66

27 Lau CP, Mehta D, Toff WD, Stott RJ, Ward DE, Camm AJ. Limitations of rate response of an activity-sensing rate responsive pacemaker to different forms of activity *PACE* 1988;11:141–6

28 Gillette P. Implantable sensor for closed-loop prosthetic systems In: Ko WH, Mugica J, Ripart A, eds. *Critical analysis of sensors for physiological rate responsive pacing* Mount Kisco, NY. Futura, 1985.251–6

29 Lau CP, Wong CK, Leung WH, Cheng CH, Lo CW A comparative evaluation of minute ventilation sensing and activity sensing adaptive-rate pacemakers during daily activities. *PACE* 1989;12 1514–21

30 Baig W, Sutcliffe R, Green A, Perrins CJ. Initial experience with slope adaptation in the Tx 919 QT sensing pacemaker [Abstract]. In. *Proceedings of 4th symposium on cardiac pacing*. Stockholm: Elsevier, 1989.104

31 Alt E, Heinz M, Hirgstetter C, Emslader HP, Daum S, Blomer H Control of pacemaker rate by impedance based respiratory minute ventilation *Chest* 1987;92 247–52

32 Occhetta E, Prando MD, Perucca A, *et al.* Respiratory pacemaker dysfunction. 4 years follow-up. In: Santini M, Pistolese M, Alliegro A, eds. *Progress in clinical pacing* Rome, 1986:77

33 Wertheimer L, Hassen AZ, Delman AJ. The 24 hour (circadian) rhythm of the cardiovascular system. *Clin Res* 1972,20 404–11

34 Stangl K, Wirtzfeld A, Heinze R, *et al* A new multisensor pacing system using stroke volume, respiratory rate, mixed venous oxygen saturation, and temperature, right atrial pressure, right ventricular pressure, and dP/dt *PACE* 1988,11:712–24.

Br Heart J 1990;64:32-5

TECHNOLOGY

Percutaneous transluminal coronary angioplasty: catheter technology and procedural guidelines

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In the April issue of the *British Heart Journal* de Feyter *et al* from the Thoraxcenter described their angioplasty experience with the monorail technique in 1000 patients.[1] The results were excellent with success in 92% of cases and major complications in only 3·3%. They concluded that the monorail technique is safe and effective but, in the absence of a randomised trial, were careful to avoid firm statements about how it compares with other techniques. A randomised trial would be a formidable and perhaps impossible undertaking for the reasons discussed in de Feyter *et al's* paper. Without this information to guide the selection of angioplasty equipment, most operators pragmatically use a limited selection of familiar catheters, experimenting with something new only if it seems to offer special advantages.

New technology should be judged by its ability to improve the results of angioplasty by solving specific procedural problems. Early reports identified inability to cross the coronary stenosis as the commonest cause of failed angioplasty and this prompted the introduction of the steerable guide wire, which substantially improved matters by increasing rates of passage from 78 to 92% in the National Heart, Lung, and Blood Institute Registry report.[2] There remained, however, a considerable number of cases in which, though the stenosis was crossed with the guide wire, it proved impossible to pass the stenosis with the tip of the balloon catheter either because the stenosis was too tight or because it was located distally in the coronary vessel. Manufacturers responded by developing guide wires and catheters with ever more favourable mechanical characteristics[3] so that this too has become an unusual cause of failure. Attention is now being directed towards treatment of the chronically occluded vessel and success rates are already improving though there is less optimism about finding purely technological solutions to the problems of coronary reocclusion and restenosis—developments in pharmacology are expected to be as important as technology.

This article summarises currently available angioplasty technology and attempts to provide guidelines for selection of catheters and guide wires.

Angioplasty technology

GUIDING CATHETER

Guiding catheters have an outer polyurethane (or polyethylene) layer providing stiffness and memory, an underlying wire matrix for transmission of torque, and a luminal lining of Teflon. They are larger than conventional diagnostic catheters with a relatively short non-tapered tip to accommodate the dilatation system; they are also stiffer to provide back up and support. These features all increase the risk of damage to the intima at the coronary ostium, particularly during deep superselective engagement. The risk is only partially offset by provision of a soft catheter tip, and considerable care is necessary if these catheters are to be used safely.

The catheter is required to provide a stable platform for the advancement of the dilatation balloon. The lumen must be large enough not only to accommodate the dilatation system but also to deliver contrast and for pressure monitoring. 9F catheters may be required for complex angioplasty with simultaneous introduction of twin dilatation catheters but for most cases large lumen (up to 0·079 inch) 8F catheters are preferred because they engage more comfortably with less risk of intimal damage or complications at the arterial puncture site. Side hole catheters are available to preserve perfusion pressure in the event of coronary wedging, but because they allow contrast spillage into the coronary sinuses visualisation is less satisfactory.

DILATATION CATHETER

Essential components of the dilatation catheter are the shaft with at least one central lumen for inflation of the distally located balloon. The guide wire may be fixed at the tip of the catheter ("fixed wire" system) but more commonly "over the wire" systems are used, requiring a second lumen for the guide wire running the length of the catheter. In the monorail catheter, however, the second lumen is confined to a short (17–25 cm) track at the distal end and the guide wire provides a "sliding rail" along which the catheter can be passed.

Balloon technology

Various balloon polymers are used including polyvinyl chloride (USCI), polyethylene (ACS, Medtronic), polyolefin copolymer (SciMed), and polyethylene terephthalate (USCI). The distensibility, pressure capability, profile, and friction characteristics of these materials are different. Distensibility depends on the compliance (pressure/volume relation) of the polymer, and polyethylene terephthalate (unlike the other commonly used balloon materials) is non-compliant, maintaining a relatively constant balloon size over a range of inflation pressures. The greater compliance of the other balloons causes them to enlarge beyond their nominal size as inflation pressure rises. This has the advantage of allowing a slightly undersized balloon to be used to reduce the risk of dissection, while leaving scope for an increase in balloon size by high pressure inflations later in the procedure to reduce residual stenosis without having to exchange the dilatation catheter.

The pressure capability of the balloon depends upon its inherent strength and thickness. Polyethylene terephthalate is the strongest balloon polymer, permitting a balloon wall thickness of only 0·0002 inch compared with the 0·002–0·003 inch required for other materials. Thus polyethylene terephthalate balloons are low profile but have the disadvantage of increased fragility making them susceptible to damage during handling. Polyolefin copolymer is second to polyethylene terephthalate in terms of polymer strength but because balloons made of this material have thicker walls they are able to sustain higher inflation pressures, approaching 12 atmospheres for the SciMed "Strong" catheter. This is useful for adjusting the balloon diameter for sizing purposes (see above) and also makes the polymer suitable for unyielding calcified stenoses when high pressure inflations may be necessary. The low burst strength of polyvinyl chloride and polyethylene balloons makes them less appropriate for lesions of this type.

The transverse diameter of the deflated balloon is an important determinant of whether a tight stenosis can be crossed, and manufacturers place great emphasis on it, advertising the lowest possible value often without any indication of how it was derived. As previously stated, polyethylene terephthalate balloons have potentially favourable profile characteristics (0·031 inch transverse diameter for the USCI Mini-Profile 2·0 mm balloon) although the balloon attachments may add 0·003 inch to the stated profile. These balloons, however, have no "memory" and may bunch while crossing tight stenoses. Polyvinyl chloride balloons have a different problem, tending to "wing" after an initial inflation and completely altering their profile characteristics. Balloons made of polyethylene and polyolefin copolymer have a better intrinsic memory and they retain their low profile wrap with repeated inflations. These polymers also have a lower coefficient of friction than polyvinyl chloride, and the Microglide coating now applied to the ACS polyethylene balloons has reduced friction still further, easing their passage through tortuous vessels and tight stenoses. Other manufacturers are applying similar lubricants to their balloon catheters.

Catheter technology

Over-the-wire systems are the most widely used with either eccentric or concentric lumens. The eccentric design provides a larger channel for the guide wire, facilitating distal injection of contrast and measurement of the transstenotic pressure gradient. Neither of these facilities is essential, however, and the more compact concentric design sacrifices both for a lower shaft profile and faster balloon inflation and deflation. The lower the shaft profile the better the visualisation provided by proximal injection of contrast through the guiding catheter (a feature of special importance in the current era of complex multivessel angioplasty). Over-the-wire dilatation catheters are now available with shaft diameters as small as 3·5 F (SciMed Skinny, USCI Mini-profile, Medtronic Thruflex) tapering to 3·0 F distally (SciMed Skinny). Catheter shafts are made of polyethylene in most cases, a flexible compound that provides maximum "trackability" for reaching stenoses throughout the coronary tree. Polyvinylchloride is also used (USCI, except Simplus and Mini-Profile). This is stiffer and provides more "pushability" for advancing the catheter across tight stenoses. Generally speaking, however, pushability is bought at the expense of trackability and catheters (for example Profile Plus, Trac Plus) are now available with a polyvinylchloride shaft and a flexible neck behind the balloon, which to some extent combine both features. Recently available is the low profile Medtronic Thruflex catheter which has a novel spring-coil, polyethylene coated, shaft with an extra flexible distal segment combining pushability and trackability.

The Schneider monorail catheter has a polyvinylchloride shaft and comes with both polyethylene terephthalate and polyvinylchloride balloons. The guide wire lumen is restricted to the distal 17 cm where the shaft diameter is 3·6 F. The remainder of the shaft has a single inflation-deflation lumen and, consequently, a very low profile (3·0 F). The ACS RX catheter has a similar design with a slightly longer guide wire lumen (25 cm). Probably the major advantage of the monorail system is that it allows for the guide wire to be directed into the coronary artery before the catheter is introduced. This facilitates guide wire control during this critical stage of the procedure and ensures excellent visualisation from proximal injections of contrast. Once the guide wire is in place, the catheter can be run along it and positioned across the stenosis. So long as the guide wire is in position, access to the coronary artery is preserved and multiple catheter exchanges can be performed as necessary. Disadvantages of the monorail catheter include some loss of axial support which reduces pushability, though this problem has been partially resolved by lengthening the guide wire lumen from 9 cm to 17–25 cm.

Fixed guide wire catheters have a single inflation-deflation lumen with a very low shaft profile. The most widely used has been the USCI Probe which has a Teflon coated 1·7 F steel shaft with a polyethylene neck and a polyethylene terephthalate balloon (transverse diameter of deflated balloon only 0·20 inch for a

2 0 mm balloon). The distal wire tip is 0·014–0·016 inch in diameter and either 1 or 2 cm long. The profile characteristics of the Probe and other fixed wire systems (for example SciMed ACE) ensure excellent visualisation and often enable high grade distal stenoses to be crossed. Moreover, these catheters can be used alongside conventional over-the-wire systems within the same 9 F giant lumen guiding catheter and are ideal for complex procedures requiring simultaneous dilatations of branch stenoses ("kissing balloon" technique; see below). The absence of a removable guide wire has important disadvantages, however; if a larger balloon size is required the catheter cannot be exchanged as safely as an over-the-wire or monorail catheter, torque transmission is poor (which makes steering difficult), and it may be impossible to advance the balloon across the stenosis if the tip of the wire jams in the distal vessel wall.

GUIDE WIRE

Guide wires for percutaneous transluminal coronary angioplasty range in diameter from 0·010 to 0·018 inch and are usually Teflon coated to reduce friction within the catheter and coronary artery. ACS wires also come coated with Microglide to improve friction characteristics further. Full body wires in which the core extends to the tip have greatest torque control (steerability), are easy to shape, and provide maximal axial support, which is particularly useful for crossing totally occluded vessels. However, because these wires are stiff and liable to damage the intima, floppy guide wires in which the core stops 2–3 cm short of the tip are preferred for most cases. The 0·014 inch floppy wires from ACS and USCI are the most widely used and if properly shaped can be guided across stenoses throughout the coronary tree.

It is now generally accepted practice in percutaneous transluminal coronary angioplasty that guide wire access for catheter exchange should be continuously available until the procedure is safely completed. In the past this demanded removal of the standard guide wire and substitution of a 300 cm exchange guide wire for each catheter exchange. The procedure was cumbersome but now is rarely necessary with the introduction of extendable guide wires in which the extension is attached to the standard guide either by a screwing (USCI) or docking (ACS) mechanism. Use of the monorail technique, of course, avoids the problem altogether because the standard guide wire is used as a sliding rail for catheter exchange.

A more recent development in guide wire technology has been the SciMed dilating guide wire (DGW) with a 1·5 mm balloon and a 3 cm flexible tip that will pass through the lumen of the Trac or Trac Plus dilatation catheters. This allows predilatation of tight stenoses before the balloon catheter is advanced to complete the procedure.[4] Though this technique is theoretically attractive, experience is limited and its value remains to be established.

Procedural guidelines

In planning an angioplasty procedure, the operator must select the guiding catheter, dilatation catheter, and guide wire most appropriate to the case in hand. The choice will be influenced largely by personal experience, and a limited range of familiar equipment will be satisfactory for most procedures.

The guiding catheter is critical to the success of the procedure and if it is not firmly seated in the coronary ostium and directed along the axis of the diseased artery the chances of traversing a tight stenosis or occlusion are considerably reduced. Most operators prefer the femoral approach with conventional Judkins catheters, particularly for procedures in the left anterior descending and right coronary arteries; an Amplatz catheter often provides better direction and support for circumflex lesions. Nevertheless, for shepherd's crook right coronary arteries or other anatomical variants alternative guide catheters may be necessary and in such cases the brachial approach is sometimes better. Side hole catheters are rarely necessary for angioplasty of the left coronary artery but many operators use them routinely for the right coronary artery where there is greater risk of catheter wedging and interrupting coronary perfusion. The guiding catheter is usually required to provide "passive" back up support and is positioned in the coronary ostium by conventional diagnostic techniques. In more difficult procedures, however, "active" back-up support may be required, with deep, often superselective, engagement being used to provide axial stability. This demands considerable care and should only be attempted if the proximal coronary artery is free of disease and large enough to accept the guiding catheter. Guiding catheters designed for active placement are now available (Medtronic SL series) with a long (9 cm) flexible distal segment suitable for deep engagement.

For single vessel angioplasty of a proximal stenosis equally good results can be expected from an over-the-wire or monorail system with a floppy guide wire. Because the monorail technique gives better guide wire control and visualisation some operators prefer to use it for distally located tight stenoses, though fixed wire low profile catheters are also effective.[5 6] If the stenosis lies close to an important side branch, this should first be protected by insertion of a guide wire (to provide access in the event of occlusion) before proceeding to angioplasty of the main vessel.[7] If the stenosis affects the branch vessel, many operators insert a low profile fixed wire dilatation catheter across it and a second dilatation catheter in the main vessel, inflating both balloons simultaneously (the "kissing balloon" technique).[8 9] Specially designed angled balloons are also available for stenoses at branch locations; experience with their use is limited.[10 11]

Choice of balloon size is important.[12 13] Many operators intentionally "oversize" the balloon to achieve a widely patent vessel. This may increase the risk of dissection and it is more prudent to match the balloon size to the vessel, and perhaps to use a distensible (non-polyethylene terephthalate) balloon which leaves the option for hyperinflating the balloon towards the end of the procedure if adequate dilatation has not been achieved. There is no evidence that the duration of individual inflations influences the final result though the cumulative inflation time may be a more important variable.[14,15]

Multivessel angioplasty is associated with a somewhat greater risk[16] and it is usually the policy in our hospital to stage the procedure, dilating the most critical stenosis first and, if successful, proceeding to the other lesions during a later procedure. When more than one stenosis is dilated during a single procedure, guide wire access to each stenosis should if possible be retained until the procedure is complete.

In complete coronary occlusion the results of angioplasty are less satisfactory, with success rates of between 50 and 55%.[17,18] There is evidence that the outcome is better in recently occluded vessels and in vessels with well preserved collateral flow beyond the occlusion.[18] At the London Chest Hospital a stiff guide wire (ACS 0·014 inch Hi-Torque intermediate) and a low profile, low friction catheter (ACS SULP with a 2·0 mm Microglide-coated balloon) are preferred. Maximum support for the guide wire is essential and this is usually achieved by active engagement of the guiding catheter while the dilatation catheter is advanced down the coronary artery to the occlusion. Alternative techniques are also receiving attention. The USCI 0·038 inch floppy tipped hollow guide wire and the Schneider 0 021 inch floppy tipped Magnum guide wire (with a 1 mm terminal olive) are support devices for a conventional guide wire and dilatation catheter respectively; both have been recommended for angioplasty of occluded vessels.[19,20] The Medtronic Omniflex catheter has also been recommended for this purpose.[21] This is a low profile, spring-coil, polyethylene coated catheter with a 2·9 F shaft and a 0·034 inch transverse deflated diameter for a 2·0 mm balloon. A novel feature of the catheter is the "fixed wire" tip that can be rotated and flexed by a simple control system at the proximal end. The combination of pushability and tip control presumably accounts for its value in opening up occluded coronary arteries. Acute coronary occlusion complicating angioplasty is a medical emergency for which patients may need other interventions as preludes to bypass surgery. An autoperfusion catheter can be inserted over a guide wire placed across the occlusion.[22] Multiple perforations along the distal portion of the catheter allow blood to flow into the holes proximal to the occlusion and out through the holes distal to it. This protects against ischaemic damage in the same way that injections of arterial blood through the central lumen of a conventional balloon catheter have been shown to do.[23] However, the autoperfusion catheter depends upon an adequate head of arterial pressure to function effectively and this is not always available when the catheter is needed.

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1 de Feyter PJ, Serruys PW, van den Brand M, Suryapranata H, Beatt K Short term results of percutaneous transluminal coronary angioplasty with the monorail technique experience in the first 1000 patients *Br Heart J* 1990,63 253–9
2 Detre K, Holubkov R, Kelsey S, *et al* Percutaneous transluminal coronary angioplasty in 1985–1986 and 1977–1981 The National Heart, Lung, and Blood Institute Registry *N Engl J Med* 1988,318 265–70
3 Werns SW, Topol EJ. Review of hardware for PTCA *J Interven Cardiol* 1988,1·3–14
4 Rizzo TF, Ciccone J, Werres R Dilating guidewire use of a new ultra-low-profile percutaneous transluminal coronary angioplasty system *Cathet Cardiovasc Diagn* 1989,16 258–62
5 Thomas ES, Williams O, Neiderman AL, Douglas JS, King SB Efficacy of a new angioplasty catheter for severely narrowed coronary lesions *J Am Coll Cardiol* 1988, 12 694–702
6 Dorrow G, Lewin RF, Mathiak L Probe, a balloon wire initial experience *Cathet Cardiovasc Diagn* 1988,14: 286–8
7 Bowser MA, Lozner EC, Johnson LW Simplified two-wire technique for bifurcation lesions during coronary angioplasty *Cathet Cardiovasc Diagn* 1989,16 136–8
8 Myler RK, McConahay DR, Sterzer SH, *et al* Coronary bifurcation stenoses the kissing balloon Probe technique via a single guiding catheter *Cathet Cardiovasc Diagn* 1989,16 267–78
9 Thomas ES, Williams DO Simultaneous double balloon coronary angioplasty through a single guiding catheter for bifurcation lesions *Cathet Cardiovasc Diagn* 1988,15 260–4
10 Slack JD, Pinkerton CA Complex coronary angioplasty use of extended and angled balloon catheters *Cathet Cardiovasc Diagn* 1987,13 284–7
11 Vivekaphirat V, Zapala C, Fosch AE Clinical experience with the use of the angled balloon dilatation catheter *Cathet Cardiovasc Diagn* 1989;17 121–5
12 Roubin GS, Douglas JS, King SB, *et al* Influence of balloon size on initial success, acute complications and restenosis after percutaneous transluminal coronary angioplasty *Circulation* 1988,78 557–65
13 Nichols AB, Smith R, Berke AD, Shlofmitz RA, Powers ER. Importance of balloon size in coronary angioplasty *J Am Coll Cardiol* 1989,13 1094–100
14 Faxon DP, Kelsy F, Ryan TJ, McCabe CH, Detre K Determinants of successful percutaneous transluminal coronary angioplasty report from the National Heart, Lung, and Blood Institute Registry *Am Heart J* 1984,108 1019–23
15 Timmis AD, Crick JCP, Griffin B, Sowton E Factors predictive of early angiographic and functional success following percutaneous transluminal coronary angioplasty *Eur Heart J* 1986,7 602–8
16 Deligonul U, Vandormael MG, Kern MJ, Zelman R, Galan K, Chaitman BR Percutaneous transluminal coronary angioplasty in two and three vessel coronary disease information and speculation *J Am Coll Cardiol* 1988,11 1180–2
17 Holmes DR, Vlietstra RE, Reeder GS, *et al* Angioplasty in total coronary artery occlusion *J Am Coll Cardiol* 1984,3 845–9
18 Kereiakes DJ, Selmon MR, McAuley BJ, McAuley DB, Sheehan DJ, Simpson JB Angioplasty in total coronary artery occlusion experience in 76 consecutive patients *J Am Coll Cardiol* 1985,6.526–33
19 Smith LDR, Katritsis D, Webb-Peploe MM. Use of a hollow wire to facilitate angioplasty of occluded vessels *Br Heart J* 1989,61 326–30
20 Meier B, Carlier M, Finci L, *et al.* Magnum wire for balloon recanalisation of chronic total coronary occlusions *Am J Cardiol* 1989,64 148–54
21 Hamm CW, Schofer J, Kupper W Improved recanalisation of coronary occlusions with a new catheter system *Circulation* 1988;78(suppl II) 82
22 Hinohara T, Simpson JB, Phillips HR, Stack RS Transluminal intracoronary reperfusion catheter a device to maintain coronary perfusion between failed coronary angioplasty and emergency coronary bypass surgery *J Am Coll Cardiol* 1988,11.977–82
23 Timmis AD, Griffin B, Crick JCP, Sowton E Arterial blood infusion for myocardial protection during percutaneous transluminal coronary angioplasty *Eur Heart J* 1987,8· 340–6

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AUDIT: AN INDEPENDENT REPORT

Cardiac interventional procedures in the United Kingdom during 1988

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The British Cardiovascular Intervention Society asked the cardiac units in the United Kingdom that performed adult and paediatric interventional procedures for information on the procedures that had been performed between 1 January and 31 December 1988. Information for adult procedures was obtained from 44 cardiac units, 18 of which supplied incomplete data. Information on paediatric procedures was provided by 11 units; there was no information from two units. Some units included their private patients with their National Health Service figures.

Percutaneous transluminal coronary angioplasty

Information on percutaneous transluminal coronary angioplasty was obtained from 44 cardiac units, including three private hospitals.

TOTAL NUMBER OF PROCEDURES

All units supplied this information and the final figure was 5047 (equivalent to 89 per million) for the United Kingdom. Edgar Sowton also derived a figure of 5750 for the numbers of percutaneous transluminal coronary angioplasties in the United Kingdom for 1988 (personal communication). His figures included all cases in the record books kept by the nurses of the catheter rooms in the cardiac units. This number may be an overestimate because they may include percutaneous transluminal coronary angioplasties that were not performed after control angiography. Some peripheral vessel angioplasties may have been included as coronary angioplasties. The figure from the British Cardiovascular Intervention Society may be an underestimate because the experience of medical staff in recording details for audit varies. Also it was difficult to obtain information on procedures performed in private hospitals

Table 1 Percutaneous transluminal coronary angioplasty United Kingdom 1988 (number of cases per annum in 44 cardiac units)

Cases	*Units*
0– 50	10
51–100	11
101–150	10
151–200	8
201–251	1
251–300	4

Table 2 Percutaneous transluminal coronary angioplasty 1988

Variable	*Data from*	*Mean (%)*	*(range)*
Cardiac units	44		
Total	5047		
Mortality	4817	0·77	(0–4·8)
Emergency coronary artery bypass grafting	4721	2·71	(0–6)
Myocardial infarction	3346	2·36	(0–5)
Success	4074	86·6	(56–93)

PERCUTANEOUS TRANSLUMINAL CORONARY ANGIOPLASTY: WORKLOAD OF THE CARDIAC UNITS

Table 1 shows the number of cases per annum per unit. Only 29% of the units were performing ⩾150 percutaneous transluminal coronary angioplasties in 1988.

OVERALL RESULTS OF PERCUTANEOUS TRANSLUMINAL CORONARY ANGIOPLASTY

Table 2 shows the overall results of percutaneous transluminal coronary angioplasty. The figure in the left hand column refers to the total number of procedures for which information was available. For example, out of 5047 percutaneous transluminal coronary angioplasty procedures, information on mortality was available on 4817 (95%). Mortality in these 4817 patients was 0·77% with figures for units ranging from 0% to 4·8%. Death and myocardial infarction refer to these complications occurring at or after percutaneous transluminal coronary angioplasty, during the hospital admission for the percutaneous transluminal coronary angioplasty, with or without emergency coronary artery bypass grafting. For this survey we defined success at percutaneous transluminal coronary angioplasty as the immediate angiographic result assessed visually where the stenosis was reduced to ⩽50% of the lumen of the adjacent artery. This success was achieved without complication during the admission—that is, death, myocardial infarction, or emergency coronary artery bypass grafting. Unfortunately, information on myocardial infarction and the success of the procedure was less often available from the centres. Despite the reduced information, the survey does provide an overall view of the results and complications in patients who underwent percutaneous transluminal coronary angioplasty in the United Kingdom during 1988.

SINGLE VESSEL PERCUTANEOUS TRANSLUMINAL CORONARY ANGIOPLASTY (TABLE 3)

The mortality for the procedure was low,

Table 3 Percutaneous transluminal coronary angioplasty in the United Kingdom in 1988: single vessel dilatation

	Data from	*%*	*Range (%)*
Total*	3666		
Cases of single vessel dilatation out of total percutaneous transluminal coronary angioplasties		83	63–100
Mortality	2655	0 37	0–1 9
Emergency coronary artery bypass grafting	2560	2·3	0–7
Myocardial infarction	2155	2 4	0–5 1
Success	2691	87	75–100

*There were more than 3666 cases of single vessel disease but separate information was available only on these

0 37% for 2655 patients. The immediate success rate was 87%.

MULTIVESSEL PERCUTANEOUS TRANSLUMINAL CORONARY ANGIOPLASTY (TABLE 4)

Information was available on 506 cases. The mortality and emergency coronary artery bypass graft rates were higher than for single vessel dilatation. The results reflect the increased risks for patients with more advanced coronary artery disease who were undergoing a more complicated procedure than single vessel dilatation.

Balloon dilatation of valves in adults (table 5)

Many units performed small numbers of balloon dilatations of the aortic valve. Balloon dilatation of the mitral valve was virtually confined to two units, which performed 47 out of the 60 procedures. Complications refer to significant local or general complications.

Paediatric interventional procedures (table 6)

No information was available from two units. Balloon dilatation of the pulmonary valve was the commonest procedure and it was associated with a low mortality.

Table 4 Percutaneous transluminal coronary angioplasty in the United Kingdom in 1988: multivessel dilatation

	Data from	*% (range)*
Cardiac units	24	
Total number of cases*	506	
Average number per unit	21	
Mortality	(506)	1 6 (0–5·7)
Emergency coronary artery bypass grafting	(506)	4 7 (0–16)
Myocardial infarction	(506)	3 0 (0–13)
Success (all vessels dilated)	(401)	81 (47–100)

*There were more than 506 cases of multivessel dilatation but information was available only on these.

Table 5 Balloon dilatation of valves in adults in the United Kingdom in 1988

		Death	*Complication*
Cardiac units	24		
Pulmonary valve	32	0	0
Aortic valve	136	6 (4 4%)	4
Mitral valve	60	2 (3·3%)	0
Miscellaneous			
Coarctation of aorta	7	0	0
Closure of ductus arteriosus	1	0	0

Table 6 Paediatric interventional procedures in the United Kingdom in 1988

		Death	*Complication*
Cardiac units	11		
Pulmonary valve dilatation	141	1	1
Aortic valve dilatation	56	4* (7 1%)	4
Coarctation of aorta	47	0	1
Closure of ductus arteriosus	32	0	0
Miscellaneous	61	0	0

*All neonates

Table 7 Percutaneous transluminal coronary angioplasty in 1988

Country	*No/million population*
Australia	256
Belgium	390
France	202
West Germany	233
United Kingdom	89*
United States	1000

*Figure from the British Cardiovascular Intervention Society. Other figures from Intervention Limited, 1 Redman Court, Bell Street, Princes Risborough, Buckinghamshire

Funding for percutaneous transluminal coronary angioplasty/interventional procedures

Units were asked to give details on how these procedures were funded. Very wide variation in funding was recorded. Twelve units had a separate budget, and 15 did not have a separate budget and the procedures were paid for out of the funds for cardiac catheterisation or the *x* ray department. No information on funding was available from 17 units. Of the units with a budget some had a reasonable allocation—for example £105 000 for 129 procedures. Others had a quite inadequate budget—£50 000 for 262 procedures.

Number of operators for percutaneous transluminal coronary angioplasty

Most units had two or more operators but the number of operators was not related to the number of procedures performed or the population area served.

Comments on the 1988 survey of procedures

This survey was the first attempt to audit the experience in the United Kingdom of percutaneous transluminal coronary angioplasty and other cardiac interventional procedures. It is hoped to improve the completeness of the survey in future years. The survey was made to assess the numbers and safety of the procedures. Percutaneous transluminal coronary angioplasty in 1988 in the United Kingdom was performed at relatively low risk—0·77% overall mortality and 0·37% mortality for single vessel disease. The number of percutaneous transluminal coronary angioplasties per million population in the United Kingdom in 1988 was well below the rates elsewhere in Europe and in the United States (table 7).

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BRITISH CARDIOLOGY

R M Marquis and Edinburgh cardiology

M J Godman

Robert (Bobby) Macfie Marquis

Robert (Bobby) Macfie Marquis was born in Liverpool and died on 10 August 1989 at the age of 72. Before entering medicine he trained in marine insurance acquiring habits of fiscal probity and prescience which later proved invaluable to many medical bodies who sought his advice. After graduating MB ChB in 1943 his first appointment was as house surgeon to Sir James Learmonth and his second as house physician to A Rae Gilchrist—an appointment that was to prove a formative influence on his professional career and which was the beginning of an association with Gilchrist that lasted for more than 45 years. He had an outstanding war career as a medical officer in the Parachute Regiment of the Airborne Division. He was dropped into Normandy on D Day minus one and lay buried in a ditch overnight with opposing armies passing close by. Thereafter he continued across Europe and was frequently engaged in heavy fighting. Not far from the Baltic coast he was with one of the first parties of British troops to meet one prong of the Russian army advancing along the same route from the East. After his return from the war he was awarded the Kirk-Duncan Fellowship of the Royal College of Physicians of Edinburgh in 1948. His studies at this time on "blue babies" formed the basis for his future career as a physician and cardiologist with a particular interest in congenital heart disease. He became MRCP Edinburgh in 1949 and FRCP Edinburgh in 1956. He was appointed assistant physician to the staff of the Royal Infirmary of Edinburgh in 1955 and from 1964 to 1978 was chief of the department of cardiology at the Royal Infirmary, Edinburgh.

Throughout his professional career he was deeply conscious of the debt he owed to earlier teachers and saw his responsibilities in a chain of developments stretching back via his mentor, Gilchrist, to Gibson and Meakins at the beginning of this century. George Alexander Gibson was an international authority on heart disease and was early to recognise the need to extend the investigative approach beyond the MacKenzie polygraph, which had been developed and used in general practice long before it became commercially available in 1906. Gibson's initiative was responsible for opening the first clinical medicine research laboratory in the Royal Infirmary, Edinburgh —with funds which he claimed to have been left for this purpose by an anonymous donor. Early work from the new laboratory included Ritchie's description of atrial flutter and his report of the action of the vagus in the human heart and the absence of certain murmurs in mitral valve disease. In 1919 Jonathan Meakins, a Canadian graduate who trained in cardiology with Thomas Lewis in London and in respiratory function with Holding in Oxford, was appointed to the first chair of therapeutics in Edinburgh. He proved an inspired teacher with energy and original ideas and introduced biochemical analysis and respiratory function testing to the Royal Infirmary. In 1924 Gilchrist became house physician to Meakins and his early work on oxygen therapy, paroxysmal ventricular tachycardia, digitalis dosage, complete heart block, and further experimental work in atrial fibrillation all followed from the stimulus provided by Meakins. Meakins returned to Canada to take the chair of medicine at McGill University in 1924 but had passed on the excitement and inquiry to his eager students and not least he had won the lasting loyalty and admiration of his house physician, Gilchrist.

Like Meakins, Gilchrist was a tall imposing man with unbounded enthusiasm for every facet of medicine. He was fascinated by the

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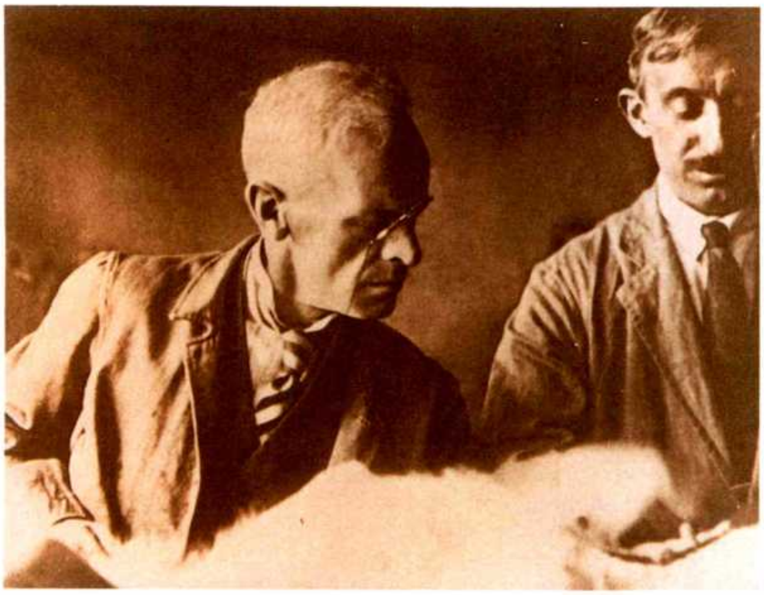
developing science of electrocardiography and recognised the importance of separate clinics for children with heart disease and for pregnant women. He became a founder member of the Cardiac Club. During this early period of Gilchrist's career the clinical medicine laboratories established and developed by Gibson and Meakins proved their worth. John McMichael returned from Aberdeen to Edinburgh as a lecturer in physiology in 1934 and in 1936 was awarded a research fellowship to work in the clinical medicine laboratory and given honorary status as assistant physician in Professor Ritchie's wards, giving him access to cardiac patients. In correspondence years later he recalls "happy days of effort and freedom to do my own thing" and "the clinical lab and its denizens as a fascinating and distinguished coterie". He followed Sir Francis Fraser (another Edinburgh graduate) to the Hammersmith Hospital when he became his assistant physician at the beginning of 1939 and was soon to extend his studies of cardiac function by cardiac catheterisation with Sharpey-Schafer. Shortly after Gilchrist's appointment in 1939 as physician in charge of ward 25 (the ward that was associated with cardiology in the Royal Infirmary of Edinburgh from Gibson's time through to Bobby Marquis) he introduced Sir John Fraser to the idea of surgical ligation of a persistent ductus arteriosus. Cardiac surgery started in the Royal Infirmary the following year, when Sir John was the first in Britain to ligate an uninfected persistent ductus. The end of the war in 1945 witnessed increasing cardiological activity all centred on ward 25 and Gilchrist. There was a changing collection of research fellows and unpaid clinical assistants until the inception of the National Health Service in July 1948 and the appointment and work of these different junior members of staff highlight the contribution of Gilchrist to so many areas of cardiology. The fellows included A D Gillanders, who made substantial contributions to nutritional heart disease; Sheila Sherlock, who subsequently went to the Hammersmith and later became a world authority on liver disease; Bobby Marquis himself; John Tulloch, a future professor of medicine in Uganda; Michael Oliver; Hamish Watson who in 1967 was to introduce into Britain balloon atrial septostomy for the management of transposition of great arteries and who in association with Emslie Smith pioneered His bundle electrocardiography in this country; James Low, a modest man with a delightful sense of humour who, in Auckland, was to become internationally recognised as one of the most able and least peripatetic cardiologists of his generation; and Olav Simpson, who held a personal chair in the department of medicine at the University of Otago. In 1953 a new department of cardiology was opened adjacent to the restricted area formerly occupied by the electrocardiographic department on the ground floor of the clinical medicine laboratory. The specialist cardiac services that had been initiated by Gilchrist in 1928 for children—and subsequently for pregnant women, ischaemic heart disease, and for cardiac surgery—were now consolidated by further senior appointments.

Gilchrist was succeeded as chief of the department of cardiology by Marquis in 1964. Three years earlier Michael Oliver who had developed an international reputation for his work in ischaemic heart disease had been appointed as physician in the department of cardiology. The vacancy created by Bobby Marquis's promotion was filled by Desmond Julian who returned to the department, where he had earlier been a senior registrar, after three years as cardiologist in Sydney, Australia. Bobby Marquis was always to recall that his major contribution to Edinburgh cardiology had been to persuade Julian to return to Edinburgh. For the next decade the work of the department was characterised by a fine blend of industry, excellence, and good fellowship. Bobby Marquis took enormous pride in the professional achievements of his two junior colleagues, Julian and Oliver. He was modest about his role in developing a department that attracted many young trainee cardiologists because it was led by a trio of individuals of quite disparate personalities and qualities—uniquely working in harmony. Many of these trainees subsequently went on to head departments in this country and abroad and he took particular satisfaction in the academic achievements of those like Ronnie Campbell in Newcastle, Valentin Fuster at the Mayo Clinic and subsequently in New York, and Keith Fox in Cardiff and as successor to Michael Oliver in Edinburgh, but his influence on those who were not high flyers was as great if not greater. His high clinical standards, his insistence on the absolute primacy of the individual patient's needs at all times, and his ability to listen attentively, conveying the impression of being totally absorbed by the problem of either patient or student (and in so doing curbing his considerable loquacious instincts), created a profound impression. He was fascinated by and delighted in people. Like many clinicians he found writing difficult. To put his thoughts, opinions, and conclusions down on paper was an enormous burden to him, whereas talking, debating, analysing, and discussing were all enormous pleasures. None the less his publications were characterised by meticulous attention to detail and he contributed important early reports on heart failure in ventricular septal defect in infancy, on unipolar electrocardiography in pulmonary stenosis, and on congenital aortic stenosis and its surgical treatment. He was fascinated by the ductus arteriosus and his Gibson lecture in 1979 reviewed 40 years of Edinburgh and personal experience in its diagnosis and management in all age groups.

His heart was given to the life and mind of Edinburgh medicine and the Royal Infirmary but he was an able and colourful ambassador for Edinburgh and British cardiology nationally and internationally. He gave unstintingly of his time to the Cardiac Society and to the *British Heart Journal*. His critiques of papers for the journal were in the form of meticulously detailed and handwritten reports whose characteristic style frustrated any attempt at anonymity if they were passed on to authors. He was a founder member of the Association of European Paediatric Cardiologists. As a schoolboy and young adult he had spent a considerable time in Germany and France and was a sound linguist and these and his other talents ensured that he played a major role in the shaping of European paediatric cardiology in the 1960s and early 1970s. But everyone who knew him will recognise that no account of his professional and other achievements can convey the impact of his extraordinary personality. All who met him were instantly enveloped in and usually enchanted by his endless enthusiasm. He had strong colourful ideas about individuals and a style that was very much his own. He delighted in and admired those who were unusually gifted and talented; but though he respected intelligence he had no time for cleverness for its own sake. He was generous in support of friends but regarded it as a duty of friendship to criticise. He drew out unlikely people. He had a particularly high regard for what he defined as "character", and above all for those who showed character in adversity. He had vast generosity of spirit to those less fortunate and less endowed than he. Those who worked with and for him and those who shared his friendship will always regard it as a privilege to have known him.

I thank Dr A R Gilchrist, now in his 91st year, for helpful suggestions. Many of the descriptions of Bobby Marquis's predecessors and contemporaries have been drawn directly from his own published account *"Cardiology in the Royal Infirmary of Edinburgh"*.

VIEWS FROM THE PAST *Ernest Henry Starling*



The physiologist in the laboratory (see also pages 4 and 22). Starling died in Kingston, Jamaica, in 1927 at the age of 61 while on a cruise intended to benefit his health, and is buried there (Lewis collection).

DENNIS M KRIKLER

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Proceedings of the British Cardiac Society

THE 69TH ANNUAL GENERAL MEETING of the British Cardiac Society was held at the English Riviera Centre, Torquay on 22 to 25 May 1990.

D Dymond was elected Honorary Assistant Secretary and S Cobbe and K A A Fox were elected to Council on the retirement of M Joy and T Treasure.

Deaths during the year: T H Crozier, R S Duff, F Gardner, P H Kidner, I K R McMillan, R M Marquis, J R W Towers, J Keith, J V Warren.

New Members 1990: P Adams (Newcastle); V Anderson (Lancaster); K Beatt (London); R Best (Cambridge); C Burrell (London); M Chopra (Cheshire); B Clarke (Southampton); I Cooper (London); M Coupe (Manchester); J Cowan (Leeds); B Craig (Belfast); D Gibbons (Penzance); J Gibbs (London); T Greenwood (London); C Handler (London); N Ineson (London); M James (Bristol); B Keogh (Harefield); R Lamb (Southampton); M Lewis (Cardiff); S Lewis (London); A Newby (Cardiff); S Pringle (Edinburgh); R Riemersma (Edinburgh); U Sigwart (London); I Simpson (London); G Thompson (London); R West (Cardiff); D Yellon (London).

New Corresponding Members: M Ballester (Spain); R Bugiardini (Italy); P Cohn (USA); M Henderson (Canada); S Weinberg (USA).

The following are abstracts of the papers that were presented.

The technique used for balloon dilatation of the mitral valve determines the size of the residual atrial septal defect: a transoesophageal echocardiography study

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Cardiac Department, King's College Hospital, London

The incidence and severity of atrial septal defects after balloon dilatation of the mitral valve have been evaluated with transoesophageal echocardiography (TOE) in 17 patients at a mean interval of 15 (range 3–30) months after the procedure. TOE in combination with colour flow mapping and during Valsalva manoeuvre was compared with similar transthoracic studies designed to detect residual atrial septal defects and transatrial flow resulting from different techniques used for balloon catheter transit and valve dilatation. In seven patients (group 1) the atrial septum was dilated with an 8 mm diameter Olbert balloon, and either a single or double balloon (Mansfield) or bifoil (Schneider) balloon was used to dilate the mitral valve. In 10 patients (group 2) the Inoue balloon, with a slimmer deflated profile, was used after dilatation of the atrial septum with a 14 French vessel dilator. In group 1 a surgically significant atrial septal defect was detected by transthoracic echo studies in one patient and transatrial flow detected by colour flow studies in five. TOE colour flow and contrast studies during the Valsalva manoeuvre detected residual transatrial flow easily in all seven patients. In group 2 patients, when the Inoue system was used, no evidence of surgically significant defects or colour flow detected defects were observed with transthoracic echo. With TOE a small defect was detected in one patient and colour flow in two. A contrast study during the Valsalva manoeuvre showed transatrial septal transit of microbubbles in all 10 patients. This TOE and conventional echo study, therefore, shows that some degree of transatrial defect persists in all patients after balloon dilatation of the mitral valve. After the use of the Inoue balloon system this is minimal, but when atrial dilatation is used significant defects are seen in all patients. TOE with colour flow mapping and Valsalva contrast studies provide a sensitive technique for detecting residual atrial septal defects after balloon dilatation of the mitral valve.

Changing indications for transoesophageal echocardiography: clinical experience in 1000 patients

N Sreeram, G R Sutherland, A G Fraser, R Geuskens, M A Taams, E Gussenhoven, J R T C Roelandt
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Transoesophageal echocardiography (TEE) is a new semi-invasive technique that should be applied only in appropriate clinical situations. We have therefore reviewed our first 1000 TEE studies carried out over 5 years to document the changing indications for TEE and to define its current role. From our first study in July 1985 (with colour flow mapping (CFM) added in the last 686 studies) the proportion of TEE studies to total annual echo studies rose progressively from 1% to 14% ($p < 0·001$). Five diagnostic areas of maximum benefit were identified. (1) Aortic pathology (19% of all TEE studies); TEE confirmed dissection morphology in 58/60 patients but missed type II dissections in two (confirmed at operation or necropsy). (2) Adolescent and adult congenital heart disease (13%); in this group TEE provided unique information on atrial situs; systemic and pulmonary venous drainage; atrial baffle function; and lesions of the atrioventricular junction, left ventricular outflow tract, and ascending aorta. (3) Mitral prosthetic valve dysfunction (10%); TEE distinguished inherent physiological regurgitation from pathological paravalvar regurgitation and showed the number and sites of pathological leakage. (4) Endocarditis (13%); TEE is of unique value in recognising retroaortic abscess cavities and fistulas. Endocarditis was diagnosed in 59% of patients studied. TEE, however, missed vegetations in six patients with prosthetic valves (proved at surgery or necropsy in four patients). (5) Intraoperative studies (15% of all TEE studies in the past three years). Though the proportion of TEE studies in patients in groups 1–4 has not changed, a relatively new indication has been the intraoperative monitoring of ventricular function and assessing mitral valve repair. Analysis of pulmonary venous flow patterns by TEE has been particularly useful in assessing valve repair procedures.

In our experience the major indications for TEE are suspected aortic dissection, endocarditis and prosthetic mitral valve dysfunction (patients with these lesions are now referred for surgery based on TEE alone), and for assessment of congenital heart disease after surgery in older patients. Its role has also expanded into intraoperative and immediate postoperative assessment of ventricular function and surgical repair and into studies in paediatric patients (53 patients).

Cerebral incidents and atrial thrombus in patients with mitral prostheses: a comparison of precordial and transoesophageal echocardiography

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Thirty eight patients with prosthetic mitral valves were studied by precordial and transoesophageal echocardiography. Ten of them were examined within five days of either a stroke ($n = 5$) or transient ischaemic attack ($n = 5$). In this subgroup (age range 43 to 76 years) four patients had metallic valves and were fully anticoagulated with warfarin (international normalised ratio 2·9–4·2); six had bioprosthetic valves and only two were anticoagulated (2·7 and 3·8). The results of both echocardiographic approaches were compared. None of the patients had clinical suggestions of endocarditis, and blood cultures were sterile. Precordial echocardiography did not detect the presence of atrial or valvular clot in any of the 38 patients. In contrast, transoesophageal echocardiography showed atrial clot in four of the 10 patients presenting with a cerebral incident and clot on the valve stent in one. Additionally, atrial appendage clot was detected in one of the remaining 28 patients who were studied for other reasons. Clot was more commonly seen in patients with bioprosthetic valves than in those with metallic valves (four out of seven *v* one out of four), and extensive atrial clot was detected in two patients with bioprosthetic valves who were not receiving anticoagulant treatment.

The results show that the presence of even extensive atrial thrombus or valvular clot cannot be excluded by precordial echocardiography in patients with prosthetic mitral valves. Study by the oesophageal route is recommended for such patients who present with either a stroke or transient ischaemic attack.

Prognostic implications of vegetations and abscess formation in infective endocarditis

M Henein, Antoninette Kenny, Cathy Fuller, Dinah Murphy, Helen Murfit, L M Shapiro
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We examined the prognostic implications of the presence of echocardiographic evidence of vegetations and abscess formation in infective endocarditis. A consecutive series of 72 patients was retrospectively identified (44 men and 28 women, age range 21–88 years). All had pre-existing valvar disease including aortic (59%) and mitral (29%) valve disease. Blood cultures were positive in 86%; the organism isolated was a *Streptococcus* sp in 47%; a *Staphylococcus* sp in 29%; and diphtheroids, *Haemophilus* sp, and *Klebsiella* sp each in two patients. Of the 72 patients, 31 had evidence of valvar vegetations (16 aortic and 15 mitral). Three patients with vegetations died; 13 required valve replacement, and 13 were successfully treated medically. A further seven (10%) patients had evidence of aortic root abscess formation (two had aortic and mitral valve vegetations also). In one an aortic Björk-Shiley valve was in situ. Despite the site of infection only one patient developed conduction disease with new right bundle branch block. One patient died and three required aortic valve surgery. The remaining 36 patients without echocardiographic evidence of vegetations and abscess formation were all successfully treated medically without complication or the need for surgery.

Echocardiography showed vegetations or abscess formation in 50% of patients with infective endocarditis and identified a subgroup with an increased risk of illness and death.

Comparative values of exercise echocardiography and ^{99m}Tc-methoxyisobutylisonitrile single proton emission computed tomography in the diagnosis of myocardial ischaemia

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The relative clinical values of exercise cross sectional echocardiography (EE) integrated with a digital cine loop acquisition system versus ^{99m}Tc-methoxyisobutylisonitrile single proton emission computed tomography need to be defined. To determine this, 80 consecutive patients with suspected myocardial ischaemia who were referred for single proton emission computed tomography were also submitted to EE during the same symptom limited bicycle exercise testing. Both EE and single proton emission computed tomography were visually analysed. For each technique three different responses to exercise were defined: (*a*) *normal* (absence of rest and exercise induced abnormalities); (*b*) *ischaemic* (reversible perfusion defect and reversible wall motion asynergy); and (*c*) *fixed abnormalities* (non-reversible perfusion defect and non-reversible wall asynergy). For analysis the left ventricle, as imaged by both techniques, was divided into six corresponding regions. Seven patients were excluded from the study because of unsatisfactory examinations: four had non-interpretable

EE and four non-interpretable single proton emission computed tomography. The presence of ischaemia was determined by EE in 31 patients and by single proton emission computed tomography in 35. In all, the response to exercise was concordantly classified in 86% (k = 0·78) of patients. Of a total of 438 ventricular regions analysed by EE and single proton emission computed tomography, 405 gave concordant results (k = 0·80). EE showed a non-ischaemic response in seven patients with positive response on single proton emission computed tomography (four patients with small posteroinferior defects and three with partial redistribution within an infarction). In three patients with an ischaemic response on EE a non-ischaemic result was obtained on single proton emission computed tomography.

EE and single proton emission computed tomography provide remarkably similar information on the presence and localisation of myocardial ischaemia. This has major implications for centres where single proton emission computed tomography is unavailable and for cost effectiveness.

Transoesophageal echocardiographic imaging in the longitudinal axis

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Thoraxcenter, Rotterdam, The Netherlands, and
National Heart and Lung Institute, London

Transoesophageal echocardiography (TE) is an established investigative technique, but its evaluation of the heart and great vessels is restricted to single transverse scan planes. A new probe has been developed that has a second transducer mounted at its tip to produce images in the longitudinal axis, orthogonal to standard transoesophageal images. The anatomical correlates of the images thus produced have not been described, and the advantages and limitations of the probe are unclear. We have therefore evaluated the biplane probe initially in 16 patients, and we have performed correlative echocardiographic and anatomical studies in three postmortem hearts. Clinical experience showed that longitudinal imaging from the stomach better demonstrates the inferior caval vein as it enters the right atrium, the left ventricular apex, and the anterior and inferior walls of the left ventricle. The left ventricular outflow tract and the proximal aorta are also visualised and are better aligned for Doppler examination. From a transducer position in the oesophagus opposite the left atrium unique longitudinal images are available of the superior caval vein, the atrial septum, the right ventricular outflow tract, the mitral valve, and the left atrial appendage and upper pulmonary vein. Ultrasonography of the mitral valve along the whole zone of coaptation is greatly facilitated by a biplane probe; the anterolateral commissure is well seen in a transverse plane, but the posteromedial commissure can be visualised only with the longitudinal plane transducer. The ascending aorta is shown by the longitudinal transducer along on average 7 cm of its length. The biplane probe cannot, however, image the whole intrathoracic aorta as the upper ascending aorta and proximal aortic arch are inaccessible to both transducers. A minor disadvantage is that image resolution is affected by the number of crystals incorporated into the two transducers. Anatomical studies suggested, confirmed, and refined the clinical interpretation of images.

Longitudinal axis TE significantly expands the diagnostic potential of TE, especially in adults with mitral valve disease or acute aortic dissection and in older patients with congenital heart disease.

Variability of serum cholesterol measurements: implications for screening and monitoring

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The reliability of screening for high serum total cholesterol concentration is adversely affected by the variability of serum cholesterol concentrations over time. This problem was investigated using data on repeated serum cholesterol measurements for 14 600 men and women in the MRC Mild Hypertension Trial. For measurements one year apart, the within person coefficient of variation (CV) was 7%, which is substantial compared with the between person CV of 15%. In a screening programme this within person variability may lead to the misclassification of subjects and to inappropriate intervention. For example, 28% of middle aged British men with a single serum cholesterol measurement above 6·9 mmol/l have a long term average cholesterol concentration below that value even without intervention. Using averages of several cholesterol measurements reduces, but does not eliminate, these problems. Furthermore, monitoring the effect of interventions in subjects by sequential cholesterol measurements may be unhelpful or even misleading.

These problems cast serious doubt on the value of screening the general population for high serum cholesterol concentrations.

Who gets coronary angiography in Scotland?

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Department of Cardiology, Western Infirmary, Glasgow, and Department of Community Medicine, University of Glasgow, Glasgow

Scotland has one of the highest incidences of coronary heart disease (CHD) in the world. Its health service is made up of 15 area health boards, which differ greatly in the provision of cardiological services. Facilities for coronary angiography are centred in four area health boards: Greater Glasgow, Lothian, Tayside, and Grampian. We examined whether or not the rate of coronary angiography was commensurate with its need, as judged by the standardised mortality rate for CHD. Data were supplied by the information and statistics division of the Common Services Agency of the Scottish Health Service on patients aged 45–64 having coronary angiography during 1985–7, amalgamated by sex and health board of residence, and compared with the standardised mortality rate for CHD in 1985. The rate for coronary angiography varied from 63·4/100 000 (Dumfries and Galloway) to 174·4/100 000 (Lothian), with comparable rates of CHD. Major differences in the rates of coronary angiography were noted in neighbouring health boards with comparable rates of CHD—for example, Greater Glasgow (169/100 000) *v* Argyll and Clyde (108·5/100 000). The correlation between rates for angiography and CHD was only r = 0·38. The rates for coronary angiography were highest in those four health boards with angiographic facilities, with the exception of Borders. The rates of coronary angiography in women correlated with that in men (r = 0·89) but ranged from 25% to 50% of that in men and tended to be lower in the outlying health boards despite similar rates of CHD.

These data suggest, as in many areas of health care, that ready access to services rather than need may be the major determinant of uptake and support the need for greater provision of cardiological skill.

Should prevention of coronary heart disease start at school?

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Children may have risk factors associated with coronary disease in adults, but data from the United Kingdom is sparse. After ethical approval we enrolled 707 11–15 year old children. Their smoking habits we obtained from a confidential questionnaire; anthropometric data, maturity, and blood pressure were measured with standard methods, and blood lipid concentrations were measured enzymatically. Physical activity was assessed by monitoring heart rate for 12 hour periods. In all, 25% had smoked, but only 11% did so regularly; 11% were overweight. Serum total cholesterol concentration was 4·59 (0·75) mmol/l, HDL-cholesterol concentration 1·39 (0·32) mmol/l, and in fasting children triglyceride concentration was 0·76 (0·43) mmol/l and LDL-cholesterol concentration 2·83 (0·65) mmol/l. Mean systolic pressure was 103 (12) mm Hg and diastolic pressure 69 (10) mm Hg. Over three days one in two girls and one in three boys failed to attain a level of physical activity conducive to cardiovascular health.

In terms of smoking, lipids, blood pressure, and low physical activity a third of the children would be defined as potentially at high risk if they were adults. Other work suggests that children retain their approximate rank order into adult life; thus emphasis in schools about the importance of adopting a healthy lifestyle might be a more effective strategy than trying to alter adult behaviour.

Excess mortality independent of age in women with acute myocardial infarction

I N Findlay, E Henderson, J Christie, C Halket, J Reid, J D McArthur, J A Kennedy, H J Dargie
Department of Cardiology, Western Infirmary, Glasgow

We compared the effects of acute myocardial infarction on mortality in men and women, in a review of 1158 patients admitted with acute myocardial infarction to our coronary care unit. Women were slightly older than men (mean age 60·7 *v* 57·1). The sites of acute myocardial infarction and incidence of previous infarction and other recorded risk factors were similar. Mean mortality was higher in women (n = 287) than men (n = 871) (23·3% *v* 9·6% respectively) at all ages (21·3% *v* 7·1%, $p < 0·0002$; 23·9% *v* 13·6%, $p < 0·005$; and 42·4% *v* 15·9%, $p < 0·02$ in those aged 50–59, 60–69 and > 69, respectively). Heart failure developed in 213/1154 patients: the mortality in patients with heart failure was 41·8% *v* 6·6% for the remainder. Heart failure occurred significantly more often in women (72/214 *v* 141/727, $p < 0·005$) and was associated with twice the mortality in men (60% *v* 32%, $p < 0·0005$).

These data show a greater risk of death from acute myocardial infarction and, in particular, an excess incidence of and death from heart failure in women compared with men after acute myocardial infarction, which is independent of age.

Ambulatory intra-arterial blood pressure monitoring in healthy individuals: differences between men and women

P Broadhurst, G Brigden, P DasGupta, A Lahiri, E B Raftery
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It has been suggested that ambulatory blood pressure monitoring is better than casual cuff methods in predicting cardiovascular events, but lack of reference data on a normal population seriously limits its clinical applicability. We therefore performed 24 hour intra-arterial ambulatory blood pressure monitoring in 50 normal volunteers (cuff blood pressure < 140/90 mm Hg) aged 18 to 74. There were 30 men and 20 women, but there were no significant differences between the sexes with regard to age, cuff blood pressure, or body mass index. A diurnal variation in blood pressure was observed, which was qualitatively similar to that in hypertensive individuals and included a prewaking blood pressure rise. Mean daytime intra-arterial pressures differed little between the sexes (124/74 mm Hg in women *v* 127/76 mm Hg in men, NS) but was lower at night in women than men (96/52 *v* 102/59 mm Hg respectively, $p < 0·02$ for diastolic pressure). Based on this group of subjects we defined the upper limit of normal daytime blood pressure in men and women as 150/90 mm Hg and that of mean night time blood pressure as 130/80 mm Hg in men and 115/65 mm Hg in women.

The lower night time blood pressures in women compared with men with similar daytime pressures may explain why women seem to tolerate similar levels of blood pressure better than men.

Follow up of glucose tolerance and insulin response in apparently healthy men in relation to coronary heart disease

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Edinburgh Royal Infirmary

Glucose intolerance or insulin insensitivity may predispose to coronary heart disease. The Edinburgh–Stockholm study showed that men in Edinburgh had a higher peak insulin concentration and a greater total release of insulin during an oral glucose tolerance test than men in Stockholm. The Scottish men ($n = 107$) were followed for 12 years, and 11 new cases of coronary heart disease were treated; five men had moved away, and the rest were invited to attend a clinic; 83 attended. All clinical and laboratory investigations were repeated. Fasting glucose, but not insulin, increased over the 12 years from 5·15 (0·06) to 6·05 (0·09) mmol/l ($p < 0.001$). The area under the glucose curve (0–120 minutes) increased from 220 (12) to 270 (18) mmol/l × minutes/l ($p < 0.01$). Body weight, subscapular and abdominal skinfold thicknesses, but not triceps skinfold thicknesses, increased ($p < 0.001$). The increase in fasting and the area under the glucose curve over the 12 years was related to the increase in body weight ($r = 0.22$, $p < 0.05$). Changes in insulin area (0–120 minutes) were related to changes in body mass or skinfold thickness ($r = 0.30$, $p < 0.01$).

None of the glucose tolerance test variables predicted new coronary heart disease events over the 12 year follow up, in contrast to classic risk factors.

Transcatheter embolisation of coronary fistulas: an alternative to surgery?

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Percutaneous transcatheter embolisation was attempted in six patients with coronary artery fistulas. The age range was 2 to 67 (median 16) years. In five patients the fistulas were congenital and in one the fistula was a complication of aortic valve replacement. The fistulas originated from branches of left (four patients) and right (two) coronary arteries and drained into the right ventricle (two), right atrium (two), coronary sinus (one), and a bronchial artery (one). Two patients (both adults) had symptoms, one dyspnoea and the other angina. Embolisation was performed with detachable balloons (three patients), multiple coils (two), and a combination of a balloon and coils (one). Angiography immediately after embolisation disclosed good position of the devices in all cases. In one patient spontaneous deflation of the balloon occurred after it had been placed in a satisfactory position, and it embolised into the pulmonary vascular bed without secondary effects. This patient was referred for elective surgery. There were no other complications associated with the procedure. Follow up ranged from 4 months to 4 years (mean 10 months). Three patients underwent Doppler evaluation and two repeat cardiac catheterisation. No residual flow was found.

Transcatheter embolisation is a safe and effective approach to treating coronary artery fistulas and should be considered as the best treatment for coronary artery fistulas.

Advantages of percutaneous balloon dilatation of the mitral valve with the Inoue system

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M Monaghan
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Percutaneous balloon dilatation of the mitral valve was performed in 51 patients by a single operator. In the first 26 patients (group A) after dilatation of the atrial septum with an 8–10 mm Olbert balloon a guide wire was passed through the left heart and stabilised in the descending aorta. A single balloon (25 mm) was used in four patients, a bifoil balloon (19 mm × 2) in six, and two balloons (15 mm × 2 or 25 + 10 mm) in 15. In the last 25 patients (group B) a 14 French dilator was used to facilitate passage through the atrial septum and the Inoue balloon system was used with incremental inflations to between 25 and 29 mm diameter. Cross sectional echocardiography and Doppler colour flow were used after each inflation to assess the immediate result in group B. Mean left atrial pressure fell from 23·2 (6·1) to 13·9 (7·0) mm Hg in group A and from 25·2 (7) to 14·0 (1·0) mm Hg in group B; both results were highly significant ($p < 0.001$). Mitral valve area echocardiographically estimated three to seven days after the procedure increased from 1·1 to 1·73 cm^2 in group A and from 1·05 to 1·95 cm^2 in group B (both $p < 0.01$). Improvement in symptoms in both groups was comparable at three to 27 months. Mean screening time (20·2 minutes) and procedure time (42 minutes) were dramatically shorter in group B compared with group A, in which the corresponding mean screening time was 61 minutes and the procedure time 105 minutes. In group A three patients developed cardiac tamponade and three transient cerebrovascular accidents with two surgically significant atrial septal defects whereas none occurred in group B patients. Two patients in each group developed important mitral regurgitation requiring subsequent mitral valve replacement.

The Inoue balloon technique has clear advantages, being more easily and quickly performed and associated with fewer serious acute complications. It should become a standard interventional technique in patients with mitral stenosis and a clear alternative to open or closed surgical mitral valvotomy.

Comparison of the results of balloon dilatation and surgical valvotomy in treating pulmonary valve stenosis

A B Houston, J Bruinnenberg, J Burns, E Murtagh,
S Lilley, R Fraser, G Olaffson
Royal Hospital for Sick Children, Glasgow

Balloon pulmonary dilatation has superseded surgical valvotomy in treating pulmonary valve stenosis. Results have shown satisfactory relief of obstruction, but before completely accepting the technique it is prudent to compare the results with those achieved by surgery.

We assessed the residual gradient and severity of regurgitation by ultrasonography in 30 patients who had had balloon dilatation for isolated pulmonary valve stenosis and in 28 who had had surgical valvotomy in the preceding period; thus follow up in the balloon dilatation group was shorter than in the surgical. The valve gradient was obtained by Doppler ultrasonography, and the severity of regurgitation was assessed from the right ventricular size and colour Doppler demonstration of backflow towards the valve not through it.

The valve gradient distribution before intervention was statistically comparable in the two groups. In the surgical group it was reduced from 62 (25) to 13 (6) mm Hg after a follow up of 5·3 years and in the balloon dilatation group from 65 (25) to 25 (15) mm Hg after a follow up of 1·9 years. The difference was statistically significant but not clinically important. The degree of regurgitation from both right ventricular size and Doppler backflow was significantly greater in the surgical group than in the balloon dilatation group.

Surgical valvotomy produces greater reduction of gradient, but this is not clinically important and is achieved at the expense of a greater degree of pulmonary regurgitation. Long term implications of this are not yet known, but the study supports the continued use of balloon dilatation.

Advantages of immediate surgical standby for coronary angioplasty

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The level of surgical cover for percutaneous transluminal coronary angioplasty (PTCA) is widely debated and ranges from full standby to a team at a remote site. Our practice has been to have a team on standby with a vacant operating theatre adjacent to the cardiac catheter laboratory. From 1984 to 1989, 1262 vessels were dilated in 1032 patients (mean age 53) with a primary success rate of 90% and restenosis rate of 21%. Of these patients, 38 (3·7%), five women (mean age 55·8) and 33 men (mean age 53·0), were referred for urgent surgical revascularisation after a complication of PTCA, 36 direct to operation, and two within 24 hours. All survived surgery; 5/38 had a previous PTCA to the same vessel, and one had previous coronary artery grafts; 4/38 had PTCA for unstable angina; 18 had single, 13 double, and 7 triple vessel coronary artery disease. The vessel damaged at PTCA was the left anterior descending (LAD) artery (n = 23, 15 dissection and eight occlusion); right coronary artery (n = 9, six dissection and three occlusion); circumflex (CX) artery (n = 3, one probable air embolus and two occlusion); and LAD and CX arteries (one occlusion). Five patients required external cardiac massage into the operating theatre, two of whom had a left main stem occlusion. Four patients received internal mammary grafts and 60 reversed saphenous grafts (1·6/patient). Complete revascularisation was achieved in 94·7% of patients. The operation was performed on the fibrillating heart in nine patients, and cardioplegia was used in 29. Mean aortic cross clamp time was 33 minutes. Inotropic support was necessary for weaning from cardiopulmonary bypass in 9/38 (23·6%), and no patient required an intra-aortic balloon. Q wave myocardial infarction occurred in 6/38 (15·8%). One orthotopic transplant was performed in a patient whose LAD artery became occluded 72 hours after PTCA and who developed cardiogenic shock. The final outcome was: none dead; three patients with angina; one late death, one cerebrovascular accident, one late operation for a new LAD artery lesion; and two patients receiving diuretics or an inhibitor of angiotensin converting enzyme, or both. A further five patients died without referral for surgery (0·48%); three had salvage PTCA for inoperable disease, one had a cerebrovascular accident three hours after the PTCA, and one died suddenly 24 hours after PTCA owing to acute occlusion.

We believe that the immediate availability of surgery for most patients has been largely responsible for the zero surgical mortality and low morbidity.

Coronary angioplasty in recipients of orthotopic cardiac transplants

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The long term survival of heart transplant recipients is limited by the development of coronary occlusive disease (COD). COD is the main cause of graft failure after the first year of transplantation. It is unclear whether percutaneous transluminal coronary angioplasty (PTCA) of epicardial coronary lesions in these patients will produce prolonged arterial patency or improved graft function. Eight patients from our orthotopic cardiac transplant programme had PTCA attempted on 13 lesions up to December 1989. All had significant (70%) stenoses: five stenoses affected the left anterior descending artery; three the right; two the left circumflex; and there were three branch lesions. Primary angiographic success was achieved in 10 of the 13 lesions (71%) with a mean reduction in severity from 81·8 (SE 2·9)% to 12·5 (2·5)%. The guide wire could not be advanced across three lesions in two patients. No acute complications occurred. The mean angiographic follow up consequently is 12·6 (range 4–25) months, and the recurrence rate per lesion is 30% at present. There has been a subjective reduction in breathlessness in 57% of the successfully treated patients.

PTCA is technically possible in patients with COD after cardiac transplantation. In the short term PTCA offers improvement in arterial patency in cardiac transplant recipients comparable to that in ordinary atherosclerotic coronary disease. Long term improvement in arterial patency, reduction of symptoms, or graft survival remains unclear.

Isolated stenosis of proximal left anterior descending coronary artery: Is angioplasty the treatment of choice?

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Patients with isolated, proximal left anterior descending coronary stenoses have a less favourable prognosis than patients with other forms of single vessel disease. We report the short term and long term results of coronary angioplasty in 295 patients with single vessel disease involving the proximal third of the left anterior descending artery. Before angioplasty 76·6% had severe angina, and myocardial infarction had occurred in 27·5%. During the early part of this series non-steerable catheters were used and the angiographic success rate was 83·4% for all patients, but 90·5% for non-occluded vessels treated since 1985. Major complications included myocardial infarction (4·7%) and emergency surgery (3·4%), and clinical success at hospital discharge occurred in 79·7%. Follow up for up to 8 (median 2·9) years was 99·7% complete at census. Five years after successful angioplasty cumulative cardiac survival was 96·2%, and freedom from cardiac death and non-fatal myocardial infarction was 93·5% (95·6% and 89·4% respectively on analysis by intention to treat). Within five years after successful procedures 11·4% had coronary bypass surgery and 17% required repeat dilatation. Freedom from all cardiac events at five years was 73·8% after successful angioplasty but 63·0% on analysis by intention to treat. At census 73·6% were free of angina, 42·8% were not receiving regular treatment for angina, and 66·2% were employed.

These results suggest that coronary angioplasty is an effective treatment option for patients with symptomatic, isolated, proximal left anterior descending coronary disease.

Abnormal circulatory reflexes in hypertrophic cardiomyopathy

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In hypertrophic cardiomyopathy (HCM) exercise hypotension is found in a third of patients despite an increasing cardiac index. Abnormal peripheral vasodilatation during supine exercise is associated with exercise hypotension ($r = 0{\cdot}95$), suggesting a disturbance of vascular control mechanisms. To evaluate autonomic cardiovascular reflexes we measured changes in blood pressure (BP) and heart rate (HR) in response to Valsalva manoeuvre, posture, and respiration in 30 patients with HCM who had stopped treatment. Patients were aged 14–71 (mean 40). Blood pressure was measured intra-arterially with simultaneous electrocardiographic recording. Patients performed the Valsalva manoeuvre by supporting 35 mm Hg for 15 seconds. During the Valsalva manoeuvre 14 patients had < 15% increase in diastolic BP, suggesting impairment of baroreflex. Nine patients had < 20% increase in HR in response to a fall in pulse pressure > 20 mm Hg, six of whom also had impaired rise in diastolic BP. Five patients had a Valsalva ratio of longest to shortest RR interval < 1·41, implying impaired response. Nine had a reduced HR response to standing with a ratio of change in HR < 1·04. Twelve had a mean HR change from inspiration to expiration over six respiratory cycles < 15 breaths/minute of whom nine also had impaired Valsalva responses. Impaired autonomic reflexes were associated with non-sustained ventricular tachycardia but not with other clinical, echocardiographic, or 48 hour electrocardiographic variables; increase in HR and the ratio of percentage increase in diastolic BP to that in HR with Valsalva manoeuvre were less in patients with ventricular tachycardia (16 (11) *v* 33 (17), $p < 0{\cdot}03$, 0·9 (0·7) *v* 0·3 (0·2), $p < 0{\cdot}01$ respectively). Similarly, respiratory reflex and postural change in heart rate reflex were less (10 (5) *v* 17 (6); 1·2 (0·2) *v* 1·0 (0·06), $p < 0{\cdot}04$) in those with ventricular tachycardia.

These data suggest that impaired autonomic function is common in HCM and is strongly associated with a recognised marker of increased risk of sudden death.

Abnormal baroreceptor sensitivity in hypertrophic cardiomyopathy

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Exercise hypotension has been shown in about a third of patients with hypertrophic cardiomyopathy (HCM) and is due to a fall in systemic vascular resistance despite an increasing cardiac output. Abnormal peripheral vascular responses correlate with exercise hypotension ($r = 0{\cdot}95$) and are strongly associated with young age and a family history of sudden death. To examine the relation between inappropriate peripheral vasodilatation and baroreceptor sensitivity 27 consecutive patients aged 14–71 (mean 41) with HCM were evaluated. Peripheral vascular responses were assessed by forearm plethysmography with a mercury in silastic strain gauge. A mean of five recordings was made at rest and at peak of symptom limited supine bicycle exercise. Results are expressed as percentage change in forearm blood flow (FBF). Baroreflex sensitivity (BS) was assessed by incremental intravenous doses of phenylephrine (100–800 µg). The slope of the regression line relating rise in systolic blood pressure to the succeeding RR intervals (mseconds/mm Hg) was used to express baroreflex sensitivity. FBF decreased by 67 (44)% (range −174 to −23%) in 15/27 (55%) and increased by 23 (17)% (range −4 to 62%) in 12/27 (45%) ($p < 0{\cdot}001$). Baroreflex sensitivity was 12·01 (6·3) mseconds/mm Hg (range 2–23) mseconds/mm Hg in the 27 patients. In the 12 with a normal decrease in exercise FBF the baroreflex sensitivity was 9·89 (6·0) mseconds/mm Hg compared with 14·6 (5·8) mseconds/mm Hg in those with an abnormal vascular response ($p = 0{\cdot}05$). Univariate analysis showed that of 10 clinical, cross sectional and Doppler echocardiography, and ambulatory electrocardiographic variables only young age (30 (12) *v* 48 (15) years, $p = 0{\cdot}002$) was more common in patients with reduced baroreflex sensitivity. Analysis of covariance to take account of age on baroreflex sensitivity showed that the increased sensitivity in those with abnormal vasodilatation was independent of age ($p = 0{\cdot}007$).

The association of increased baroreflex sensitivity with abnormal peripheral vascular responses in young patients with HCM provides strong evidence for altered haemodynamic control as a potential mechanism for sudden death.

Clinical and prognostic significance of enterovirus infection and its persistence in myocarditis and dilated cardiomyopathy

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To investigate the role of enterovirus infection and its persistence patients with suspected heart muscle disease were prospectively evaluated clinically and with endomyocardial biopsy. Virus was detected in biopsy tissue with an enterovirus group specific hybridisation probe. One hundred and twenty three patients (mean age 44, range 6–70) were assessed. Forty one patients (34%) were positive for the presence of the virus and 79 (65%) were negative, of whom 3 had specific heart muscle disease on biopsy and were excluded from subsequent analysis. The two groups did not differ significantly in age, clinical presentation, or haemodynamic characteristics. At follow up (mean 24 months, minimum 12 months), however, patients who were positive had a decreased likelihood of survival (75% *v* 93%, $p < 0{\cdot}001$). Follow up biopsy was performed in 16 patients (six positive and 10 negative). Of the patients who were initially positive, two remained positive whereas four had become negative. This change was associated with a clinical improvement in three patients. None of the patients initially negative had become positive at repeat biopsy. These data show that patients who have enterovirus detected on endomyocardial biopsy with a hybridisation probe have an adverse prognosis. Of the patients who survive, a proportion are negative for virus at follow up biopsy. This may reflect virus clearance in this group.

These observations further implicate enterovirus in the pathogenesis and prognosis of myocarditis and dilated cardiomyopathy.

Idiopathic dilated cardiomyopathy: HLA association and relation to clinical and immunological features

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To identify genetic markers in dilated cardiomyopathy (DCM) and to relate them to clinical and immunological features we studied the frequency of HLA antigens and the presence of cardiac antibodies in a patient population from northern Italy and in controls from the same region. Eighty patients with DCM (65 men, 15 women; mean age 43 (10); mean duration of symptoms 33 (34) months) and 400 healthy blood donors (322 men, 78 women; mean age 38 (10)) were studied. Five patients were in New York Heart Association class I, 25 in class II, 48 in class III, and 2 in class IV. HLA typing (class A, B, C, and DR) was performed on peripheral lymphocytes with the microlymphotoxicity assay. The significance of the deviation of HLA antigen frequencies and the strength of associations was measured using Woolf's formulas; p values were corrected for multiple comparisons (p_c). Cardiac antibodies were detected by indirect immunofluorescence on normal human heart muscle and skeletal muscle. The prevalence of cardiac antibodies in DCM was: organ specific 33%, partially organ-specific 23%, and cross reactive with skeletal muscle 7%. Frequencies of HLA-A,-B,-C were similar in patients with DCM and in controls. There was a positive association with HLA-DR4 (17/80, 21% in DCM *v* 43/400, 10·7% in controls, p_c = 0·03; relative risk (RR) 2·30) and with HLA-DR5 (37/80, 46% in DCM *v* 126/400, 31·5% in controls, p_c = 0·03; RR 1·87) and a negative association with HLA-DR3 (10/80, 12·5% in DCM *v* 118/400, 29·4% in controls, p_c = 0·001; RR 0 36). Age, sex, symptom duration and severity, and prevalence of cardiac antibodies were similar in patients with and without HLA-DR3, DR4, and/or DR5.

Thus HLA-DR4 and HLA-DR5 are markers of susceptibility to DCM but, unlike in other autoimmune diseases, do not seem to influence antibody production or progression or severity of the disease.

Upright tilt in investigation of syncope in hypertrophic cardiomyopathy

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Syncope is a common symptom in hypertrophic cardiomyopathy (HCM) and is associated with an increased risk of sudden death, but the mechanisms of syncope remain unclear. Upright tilt, alone or combined with intravenous isoprenaline, has been used to reproduce symptoms in cases of unexplained syncope, but the potential of this investigation has not been assessed in HCM. Twenty four patients with HCM, 15 with a history of syncope and nine without, were submitted to upright tilt at 60° for 45 minutes and, if tolerated, further 10 minute tilts during infusions of isoprenaline at 1, 2, and 4 μg/minute. Electrocardiography, heart rate, blood pressure and cross sectional and Doppler echocardiography were monitored throughout. During tilt alone three patients with a history of syncope and one without showed syncope with profound hypotension, variable bradycardia (prolonged asystole in one patient) and reduced ventricular diameter and contractility on echocardiography. With isoprenaline three of nine patients with a history of syncopy and none of eight patients without developed presyncope associated with the development of high outflow tract gradients. In addition to these episodes mildly symptomatic or asymptomatic transient falls in blood pressure (systolic < 100 mm Hg) were noted, particularly in syncopal patients with a history of syncopy. Overall, patients with a history had a higher incidence of total hypotensive episodes than patients without ($p < 0·01$).

Upright tilt in hypertrophic cardiomyopathy may reproduce syncope in some patients. The addition of isoprenaline may induce syncope in more patients but through a different mechanism. Patients with a history of syncope are more likely to develop hypotension during tilt than patients without.

Borrelia burgdorferi infection: an aetiological factor in dilated cardiomyopathy?

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The aetiology of dilated cardiomyopathy remains obscure in many cases. *Borrelia burgdorferi*, a tickborne spirochaete and the causative organism of Lyme disease, is known to produce both cardiac arrhythmias and myocarditis. Serum samples from 150 patients with suspected heart muscle disease who had cardiac catheterisation with a view to endomyocardial biopsy were examined for evidence of borrelial infection. Positive results for Lyme disease were obtained in 26 samples from 18 patients (12%) when tested by standard serological techniques for *B burgdorferi* with enzyme linked immunosorbent assay (ELISA), indirect immunofluorescence, and immunoblotting for IgG antibody. In 14 of the 18 patients (78%) there was a clinical picture of either dilated cardiomyopathy (seven) or myocarditis (seven). Myocardial histology was consistent with acute or past myocarditis in nine patients and with dilated cardiomyopathy alone in six. Of the remaining four patients, two had significant coronary artery disease and two hypertrophic cardiomyopathy. Sixteen per cent of patients with either dilated cardiomyopathy or myocarditis were positive for *B burgdorferi* compared with 6% of patients with other diagnoses ($p < 0·05$). These data show a much higher prevalence of antibody to *B burgdorferi* among patients with heart muscle disease than in the control population.

Though a direct causal relation has not been established, these findings suggest that *B burgdorferi* may be a possible aetiological agent in dilated cardiomyopathy or in patients with suspected heart muscle disease.

Mapping of gene for familial hypertrophic cardiomyopathy and analysis of genetic heterogeneity

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We have recently reported the mapping of a gene for familial hypertrophic cardiomyopathy (FHC). Linkage analysis was performed with 41 DNA probes, selected from a panel of 120 probes that identify polymorphic loci spaced throughout the genome, to identify a locus that was coinherited with disease. A DNA probe identifying a restriction fragment length polymorphism (RFLP) previously mapped to chromosome 14 disclosed two alleles which were coinherited with the phenotypic presence or absence of FHC in a family with 20 surviving affected members, 24 deceased affected members and 57 unaffected members. There were no recombinations (crossovers between the loci in meiosis). Multipoint analysis using the LINKAGE program yielded a logarithm of the odds (LOD) score of $+9·37$ at a recombination distance of zero. This is equivalent to odds of greater than 2 000 000 000:1 in favour of the FHC locus in this family being on chromosome 14 (band q1). To investigate whether the same chromosomal locus was responsible for disease in other families with FHC 62 members from three additional families were studied by electrocardiography, cross sectional or Doppler echocardiography, and linkage analysis. Twenty two family members had evidence of FHC with unexplained left or right ventricular hypertrophy, or both. Blood samples were obtained from each family member and continuous cell lines established as a source of DNA. Linkage analysis was performed using three probes, CRI-L436, CRI-L329, and pSC14, which identify polymorphisms at chromosome 14q1, to determine whether these loci are coinherited with disease states. Of the three new families, one was found to exhibit tight linkage to the pSC14 locus, with no recombinants in 13 informative meioses. The two other families, however, did not show linkage to these probes; multipoint analysis using the LINKAGE program yielded significant negative LOD scores in both families, excluding linkage to the chromosome 14q1 locus.

These data show that there is genetic heterogeneity in families with similar phenotypic expression of FHC.

Effects of acute ischaemia on calcium release channel of the sarcoplasmic reticulum: possible role in myocardial stunning

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The calcium release channel (CRC) of the sarcoplasmic reticulum (SR) is central to the control of the cytosolic calcium concentration and hence the contractile state of the heart. In this study we have investigated the effects of normothermic ischaemia on the CRC from sheep heart. Tritium labelled ryanodine is a specific marker for the CRC, and its binding to a mixed microsomal membrane fraction isolated from sheep myocardium after 0–120 minutes of ischaemia has been used to assess CRC density. Yield of the microsomal membrane fraction was unaffected by ischaemia, but a time dependent reduction in binding sites (57% (SE 5·1) after 60 minutes) indicated CRC degradation. The yield of junctional SR membranes, obtained by fractionation of the microsomal membrane fraction on sucrose density gradients, was greatly reduced by ischaemia, but single CRCs incorporated into artificial planar phospholipid bilayers from tissue subjected to up to two hours of ischaemia seemed normal and were able to bind ryanodine. The activation of proteases or the generation of oxygen derived free radicals may contribute to CRC degradation. In vitro exposure of non-ischaemic CRCs to trypsin or singlet oxygen and superoxide radicals progressively reduced labelled ryanodine binding to junctional SR vesicles and modified the activity of CRCs incorporated into bilayers. During exposure, the channels typically exhibited a transient increase in opening followed by an irreversible loss of activity.

We conclude that the CRC is a target for degradation early during ischaemia but that residual channels continue to function normally. CRC degradation may lead to increased permeability of the SR membrane during ischaemia and exacerbate cytosolic calcium overload. Subsequent reduction in the number of CRCs might impair calcium release from the SR and, therefore, contribute to the mechanism of reduced contraction in myocardial stunning.

Myocardial potassium homoeostasis during hypoxia: role of ATP sensitive potassium channels

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Potassium (K^+) is lost from the ischaemic or hypoxic myocardium with a consequent rise in extracellular K^+ concentration. The mechanism is unknown. Experiments were undertaken with arterially perfused rabbit interventricular septa (90 beats/minute, 32°C) to compare $^{86}Rb^+$ and $^{42}K^+$ fluxes under normoxic and hypoxic conditions and to determine the contribution of activation of the ATP sensitive K^+ channel to the K^+ efflux induced by hypoxia. Septa were labelled with isotope for 150 to 180 minutes, made hypoxic (substrate free) for 15 minutes, and then reoxygenated. Hypoxia caused an increased efflux of both $^{42}K^+$ and $^{86}Rb^+$. In eight control septa hypoxia caused a mean tissue net K^+ loss of 4·03 (SE 0·62) mmol/kg wet tissue after 15 minutes (determined by $^{86}Rb^+$ exchange), and this was similar to the increase in effluent K^+ ($n = 5$), indicating that the tissue net K^+ loss was due to increased efflux rather than decreased uptake. Barium (0·1 mmol/l and 1·0 mmol/l), a non-selective blocker of K^+ channels, introduced at the onset of hypoxia caused a decrease in tissue net K^+ loss of 64 (6)% ($n = 5$) and 97 (1)% ($n = 6$) respectively (both $p < 0·01$ compared with that in control septa). Glibenclamide (0·1 mmol/l), a potent blocker of the ATP sensitive K^+ channel, decreased tissue net K^+ loss by 52 (7)% ($n = 6$) ($p < 0·01$ compared with than in control septa). Neither barium (0·1 and 1·0 mmol/l) nor glibenclamide (0·1 mmol/l) affected myocardial $^{86}Rb^+$ uptake during normoxic perfusion.

These data indicate that hypoxia causes an increase in $^{42}K^+$ and $^{86}Rb^+$ permeability and that part of the K^+ efflux from the myocardial cells induced by hypoxia may be attributed to activation of ATP sensitive K^+ channels, though other mechanisms are involved.

Dual control of tissue factor messenger RNA in human endothelium

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Tissue factor (TF) is the essential cofactor for activating the extrinsic pathway of coagulation by factor VII. In epidemiological studies raised factor VII concentrations correlate with an increased risk of cardiovascular events. Factor VII circulates in plasma whereas under normal circumstances TF is not expressed on the surface of cells that have contact with the blood. Two intravascular cell types (monocytes and endothelium), however, may be induced to express TF. The control of TF expression in these cells is clearly of crucial importance. Total RNA was extracted from human umbilical vein endothelial cells (HUVEC) that had been exposed to bacterial lipopolysaccharide (LPS) 10 μg/ml or phorbol ester (PMA) 10 ng/ml. Northern blot analysis with pantisense RNA probes labelled with phosphorus-32 showed rapid induction of TF messenger RNA (mRNA), detectable by 30 minutes and maximal at two hours after stimulation. In nuclear run on transcription assays nuclei from HUVEC exposed for one hour to either LPS or PMA showed a 10-fold increase in the level of transcription with PMA whereas little change was seen with LPS. Experiments to ascertain the half life of the mRNA with actinomycin D showed a 12-fold difference in the half-life of TF messenger RNA in cells exposed to LPS for either one or four hours ($t_{\frac{1}{2}}$ = 2 hours, 10 minutes respectively). This suggests that LPS exerts its effects by increasing TF mRNA stability. In support of this cycloheximide produces rapid induction of TF mRNA without affecting the level of transcription.

Therefore TF messenger RNA concentrations in HUVEC are controlled by changes in the level of transcription or in stability of the mRNA, or both.

Endocardial factors modulate myocardial contractile performance

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Selective removal of endocardium (2 seconds' immersion in 0·5% Triton X-100) from isolated heart muscle preparations exerts an unusual type of negative inotropic effect: it reduces contractile duration and peak isometric force without altering unloaded shortening velocity. Similar changes were induced in endocardium intact ferret papillary muscles (n = 22) with 0·1 mM 8-bromocyclic GMP and with 1 μm sodium nitroprusside, 0·4 μM atrial natriuretic peptide, and 1 μM substance P, which increased cyclic GMP concentrations by 472%, 329%, and 171% respectively. Mechanical and biochemical effects of substance P were abolished by previous removal of endocardium or by haemoglobin (10 μmol/l), which inhibits endothelium derived relaxing factor (EDRF) (n = 11). Removal of endocardium, however, did not alter the cyclic GMP content (n = 6). Bioassay of the effect of effluent from superfused cultured porcine right ventricular endocardial cells on mechanical performance of pig coronary artery rings denuded of endothelium or ferret papillary muscles denuded of endocardium showed endocardial release of (*a*) a vasodilator identical to EDRF (n = 20) and (*b*) an unidentified stable substance (not endothelin), which reversed the mechanical effects of removal of endocardium (n = 6).

Thus endocardium can influence myocardial contraction by tonic release of a substance prolonging contraction and stimulated release of an EDRF-like factor abbreviating contraction.

Abnormal expression of class II major histocompatibility complex molecule on endocardium and cardiac endothelium: a marker of immune activation in dilated cardiomyopathy

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The inappropriate expression of major histocompatibility complex (MHC) class II molecules on endothelial and epithelial cells is a recognised marker of autoimmune disease. Expression of MHC molecules was studied in dilated cardiomyopathy (DCM) to investigate the role of autoimmunity in this condition. Fresh right ventricular endomyocardial biopsy tissue from 29 patients with DCM was compared with myocardium obtained at the time of cardiac surgery from 63 patients with other acquired cardiac disease and from 22 with congenital heart disease. Conventional immunofluorescence with monoclonal antibodies to lymphocytes and macrophage markers and to MHC class II molecules was performed. Double immunofluorescence with antibody to human factor VIII was used for identifying endothelial cells. MTC class II molecules were not found on myocytes in specimens from patients with congenital heart disease and were uncommon on endothelium (3/22) and endocardium (2/22). Class II molecules were expressed more frequently in DCM than in other acquired cardiac diseases on endothelium (28/29 *v* 19/63, $p < 0{\cdot}001$) and on endocardium (22/29 *v* 11/63, $p < 0{\cdot}001$) but were not expressed on myocytes. The finding of inappropriate expression of MHC class II molecules in DCM was not related to the presence of circulating organ specific cardiac antibodies, duration of symptoms, or their severity. In all the biopsy specimens examined from patients with DCM there was a hierarchy of class II subloci product expression (DR > DP > DQ); lymphocytic infiltrates and macrophage clusters were not seen.

The finding of inappropriate expression of MHC class II molecules on endocardium and cardiac endothelium in DCM suggests a possible pathogenic role for these cells in the initiation or perpetuation of this condition, or both.

Lack of relation of pretreatment streptokinase resistance titres and streptokinase IgG concentrations with hypotensive responses and coronary patency with thrombolytic agents containing streptokinase

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One hundred and twenty eight patients (101 men, 27 women, age range 31 to 70) were treated with either streptokinase (SK) 1·5 MIU infused over 60 minutes (n = 64) or anistreplase (A) 30 units by 5 minute injection, within six hours of onset of acute myocardial infarction. Pretreatment blood samples were analysed for streptokinase resistance titre (SKRT) in 96 patients (48 receiving SK, 48 receiving A) and specific SK IgG concentrations in 124 (60 receiving SK, 64 receiving A). Median IgG concentrations for each treatment group were similar (SK 1·19 *v* 1·04 μg SK binding/ml, NS), but the median SKRT was significantly higher in the A group (50 *v* 20 IU SK/ml, $p < 0·05$). Blood pressure was recorded at two minute intervals for 90 minutes after treatment. In the SK group 23/64 had a hypotensive response (defined as a blood pressure fall of at least 20 mm Hg lasting at least 6 minutes): 20 within the first 30 minutes, nine after 30 minutes, and six both. In the A group 33/64 had a hypotensive response: 26 early, 13 late, and six both (NS). Angiographic coronary artery patency was 53% and 55% (NS) at 90 minutes with SK and A respectively and 87·5% and 81% (NS) at 24 hours. The infarct related artery was: left anterior descending (54 patients), right coronary (55), circumflex (12), and not determined (seven). No significant relation was found between pretreatment SKRT or SK IgG concentrations and coronary patency or hypotensive responses, nor between the infarct related vessel and hypotensive responses.

Therefore these indices of previous exposure to streptococcal protein do not influence the thrombolytic efficacy or likelihood of hypotensive response to these SK containing thrombolytic agents, and the site of infarction is not related to hypotensive responses.

Placebo controlled trial of xamoterol versus digoxin in chronic atrial fibrillation

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Twelve patients with chronic atrial fibrillation and normal resting heart rate but exercise tachycardia and bradycardic episodes were randomised to receive xamoterol 200 mg twice daily, digoxin, or placebo in a double blind crossover study. Patients were assessed by symptom scores for dyspnoea, fatigue, and dizziness and by 24 hour ambulatory electrocardiographic monitoring and treadmill exercise testing. Maximum and minimum hourly heart rates and number and duration of ventricular pauses were measured. Combined symptom score results for xamoterol (4·9) were significantly lower than for digoxin (6·2) or placebo (6·2), ($p < 0·05$). Resting heart rate before exercise was lower (62 (5) beats/min) with digoxin than xamoterol (72 (5) beats/min), ($p < 0·005$) or placebo (70 (5) beats/min), ($p < 0·01$). Resting heart rate did not differ between placebo and xamoterol treatments. Maximum exercise heart rate was significantly slower with xamoterol (136 (10) beats/min) than with digoxin (150 (10) beats/min), ($p < 0·005$). Xamoterol increased the minimum hourly heart rate from 50 (4) to 59 (5) beats/min, ($p < 0·05$) but reduced the maximum hourly rate from 139 (8) to 132 (8) beats/min (NS). Digoxin reduced maximum heart rate to an equal extent (132 (8) beats/min (NS)) whereas the minimum heart rate declined (45 (3) beats/min, $p < 0·001$) compared with xamoterol. Xamoterol significantly reduced the maximum duration of ventricular pauses (1·8 (0·1) seconds) compared with placebo (2·3 (0·1) seconds) ($p < 0·005$) or with digoxin (2·5 (0·1) seconds) ($p < 0·001$).

We conclude from these data that xamoterol is effective in rate control and relief of symptoms in chronic atrial fibrillation, and may be preferable in patients with episodic bradycardia or ventricular pauses.

Effects of calcitonin gene related peptide on human coronary blood flow and epicardial vessel diameter

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Calcitonin gene related peptide (CGRP) is a potent dilator of epicardial coronary vessels in humans, but its effects on myocardial resistance vessels and coronary blood flow are unknown. The effects of CGRP on coronary artery blood flow and epicardial vessel diameter were investigated in seven patients (aged 40–57); six were men. Four had coronary artery disease, and three had normal coronary arteries. All had been admitted for routine coronary angiography for the investigation of chest pain. Left anterior descending vessel diameter, coronary sinus oxygen saturation (CSo$_2$S), systemic blood pressure, and heart rate were measured during intracoronary infusion of increasing concentrations of CGRP (up to 200 ng/ml at 2 ml/minute), followed by intracoronary adenosine (10^{-6} M at 2 ml/minute), and, finally, intracoronary glyceryl trinitrate (GTN) (5 μg/ml at 2 ml/minute). CGRP dilated the left anterior descending artery by a mean of 23·0% (95% confidence interval ±6·6%) $p < 0·001$, with only a small increase in CSo$_2$S from 40·1 (±7·8)% to 47·3 (±5·1)%, $p < 0·001$. Adenosine, a potent dilator of myocardial resistance vessels, caused no further increase in epicardial vessel diameter but a rise in CSo$_2$S from 47·3 (±5·1)% to 76·0 (±5·8)%, $p < 0·01$. GTN caused no further increase in epicardial vessel diameter. Myocardial work as assessed by heart rate × blood pressure product remained unchanged throughout the study; CSo$_2$S can therefore be used as an index of myocardial blood flow. The CSo$_2$S increased only slightly during CGRP infusion. That this rise in blood flow was not due to impaired coronary flow reserve was confirmed by the pronounced response to adenosine infusion.

These data indicate that CGRP, though a potent dilator of epicardial vessels, has little effect on myocardial blood flow in non-ischaemic myocardium in humans at rest.

Control of sick sinus syndrome by xamoterol

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Xamoterol has properties which might be beneficial in the sick sinus syndrome. We have studied its short term and long term effects on patients with mild to moderate symptoms. We entered 26 patients into a short term, double blind, randomised crossover trial of xamoterol versus placebo. Their response was assessed by symptoms, weekly Holter monitoring, and exercise testing. The 13 patients who improved were started with xamoterol for up to one year. All had symptoms, and seven had been referred for permanent pacing. Holter monitoring was repeated at three monthly intervals during treatment and again two days and two weeks after treatment was stopped. Treatment was stopped early in five patients (two required permanent pacing, one developed ventricular tachycardia, one had worsening palpitations, and one died of bronchial carcinoma). The remaining eight patients took xamoterol for nine to 12 months, and the beneficial effects on symptoms and electrocardiography were maintained. On withdrawal of the drug all six patients who had pauses while taking xamoterol displayed an increase in the number and duration of these; four noticed a deterioration in symptoms.

Xamoterol may improve sinoatrial disease for up to one year and might be an alternative to pacing in some patients.

Does antianginal treatment with atenolol, nifedipine, and isosorbide monocitrate confer more benefit than treatment with atenolol and nifedipine or isosorbide monocitrate in patients with stable angina and symptoms receiving atenolol?

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Twenty two patients with stable angina pectoris and proved coronary artery disease were evaluated subjectively and by maximal treadmill exercise testing (MET). They entered a randomised double blind crossover study of four weeks of atenolol 100 mg (A) and placebo (P), A and nifedipine slow release 20 mg twice daily (B), A and isosorbide mononitrate 20 mg twice daily (C), and all three active agents combined (D). Exercise time expressed in seconds of the Bruce protocol was significantly longer during treatment C (473 (21·2) than treatments P (427 (19·4)), B (438 (23·4)), or D (455 (22·6)) ($p < 0·05$). There was, however, no significant difference in maximum ST depression (mm) between treatment periods P (1·4 (0·70), B (1·39 (0·7), C (1·44 (0·7)) and D (1·54 (0·8)). The rate of angina attacks was reduced from 15·6 (2·3) with treatment P to 10·2 (2·2) with treatment B, to 11·3 (2·5) with treatment C, and to 12·5 (2·6) with treatment D. Nitrate consumption fell similarly.

The combinations of atenolol and isosorbide mononitrate or nifedipine slow release were equally effective with no obvious further benefit conferred by all three combined. Nitrate tolerance was not observed after four weeks of continuous treatment.

High coronary artery patency and plasma recombinant tissue plasminogen activator concentrations after bolus administration of alteplase in acute myocardial infarction

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Thirty three consecutive patients (23 men and 10 women, age range 40–74) suitable for thrombolytic treatment within six hours after onset of myocardial infarction detected on electrocardiography were treated with two intravenous boluses of 35 mg alteplase 30 minutes apart. Mean time to first bolus was 208 (75) minutes after onset of symptoms. Coronary angiography was successfully performed in 30/33 patients, starting 30 minutes after treatment with serial injections to 90 minutes and at 24 hours. The infarct related artery was left anterior descending in 12 patients, right coronary in 15, left main coronary artery in one, and circumflex in two. At first injection (49·4 (13·3) minutes) the rate of patency (TIMI grades 2 and 3) was 23/30 (77%, 95% confidence interval 61% to 92%), rising to 26/30 (87%, 74% to 99% at 90 minutes). At repeat angiography at 24 hours 24/29 arteries were patent (83%, 69 to 97%). The rate of reocclusion at 24 hours was 3/29 (10%, 0 to 22%). Five patients had haematoma formation related to arterial cannulation, and three had minor spontaneous bleeding. Mean baseline plasma recombinant tissue plasminogen activator (rtPA) concentration ($n = 24$) was 20·1 (1·5) ng/ml, attaining peaks of 4451 (452) and 4124 (450) ng/ml after the two boluses of alteplase. Before the second bolus the mean rtPA concentration fell to 415 (56) ng/ml, and 90 minutes after the second bolus it fell to 130 (23) ng/ml.

These results show that the administration of two intravenous boluses of alteplase achieves brief, high plasma concentrations of rtPA, resulting in high coronary patency without serious adverse effects on bleeding or reocclusion.

Reduced myocardial efficiency in hypertrophic cardiomyopathy

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The common symptoms of chest pain and dyspnoea in hypertrophic cardiomyopathy (HCM) are often refractory to treatment, and the mechanisms which underly them are poorly understood. The severity of symptoms and impairment of exercise capacity ($\dot{V}O_2$ max) are not closely related to the severity of left ventricular (LV) hypertrophy, to the presence of an LV outflow tract gradient, or to LV filling pressures. To investigate myocardial function at a more basic level in HCM we compared LV heat production, an index of myocardial mechanical efficiency, in five patients with HCM and five normal controls, at the time of cardiac catheterisation. All patients had normal epicardial coronary arteries. Energy supply to the myocardium, calculated from myocardial oxygen uptake, was higher in the patients with HCM compared with that in the controls (mean 6·3 (SD 2·5) W *v* 4·4 (2·5) W, NS). Proportionately more of the energy released by the metabolism of this oxygen, however, was 'wasted' as heat in the HCM group (mean LV heat production 4·6 (1·6) W *v* 2·5 (1·1) W, $p < 0·05$). Calculated myocardial efficiency was significantly lower in the HCM patients (0·23 (0·10) *v* 0·44 (0·10), $p = 0·006$).

It is not clear whether the observed reduction in mechanical efficiency of the myocardium in HCM is a consequence of the hypertrophy per se. Evaluation of the myocardium in other hypertrophic states is warranted.

Changes in human monophasic action potential during transient aortic occlusion

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The strong association between ventricular arrhythmia and ventricular dysfunction is unexplained. One possible mechanism may be a feedback limb of excitation-contraction coupling, whereby ventricular loading conditions influence the time course of repolarisation and hence refractoriness (contraction-excitation feedback). Although this has been shown in animal studies, and despite its potential arrhythmogenic importance, there is to date only limited evidence for the existence of this phenomenon in humans. We recorded monophasic action potentials during transient aortic occlusion from the left ventricular epicardium in 16 patients having routine coronary artery surgery. Peak systolic pressure was monitored using the routine radial artery pressure in 10 patients and left ventricular pressure by direct needle puncture in six. Aortic occlusion for between one and three beats was used to produce a transient increase in ventricular loading. In all patients during aortic occlusion the monophasic action potential duration at 90% repolarisation decreased (325 (SD 31) mseconds to 311 (29) mseconds, $p < 0·0001$). After release the monophasic action potential duration returned to initial values within three beats. In the six patients in whom intraventricular pressure was measured directly peak systolic pressure rose from 79 (18) mm Hg to a maximum of 139 (27) mm Hg ($p < 0·0001$) during the occlusion. In these six patients there was a strong correlation between beat to beat changes in peak systolic pressure and changes in monophasic action potential duration ($r = 0·96$, $p < 0·0001$). This study shows that changes in the timing of repolarisation in response to acute changes in ventricular loading occur on a beat to beat basis.

The results provide further evidence for the existence of contraction-excitation feedback in humans. Inhomogeneous contraction patterns could, by this mechanism, induce inhomogeneity of repolarisation and provide an ideal basis for arrhythmia.

Potassium concentration in cardioplegic solutions has a critical role in mediating endothelial damage in isolated rat heart

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We have previously shown that serotonin 5 hydroxytryptamine causes dose dependent vasodilatation of coronary circulation in isolated rat heart by releasing nitric oxide. We studied the effect of potassium concentration in cardioplegic solutions on the vasodilatation in rat heart induced by serotonin and glyceryl trinitrate (GTN). Forty eight rat hearts were perfused on a modified Langendorff preparation; after exposure to 10^{-7}M serotonin and 10 μg/ml GTN they were perfused for 30 or 60 minutes with either St Thomas's solution or Bretschneider solution containing 20 mmol/l or for 30 minutes with either solution containing 30 mmol/l potassium (eight hearts each). Serotonin and GTN caused 39·0 (3·3)% and 39·7 (2·8)% increase in coronary flow respectively. After 30 or 60 minutes' perfusion with St Thomas's solution containing 20 mmol/l potassium there was little change in response to serotonin or GTN (43·1 (4·1)%, 38 (3·2)% respectively). Similarly, perfusion with Bretschneider solution (20 mmol/l potassium) for 30 or 60 minutes did not alter the amount of vasodilatation (serotonin 39·2 (2·9)% GTN 38·0 (3·3)%). Perfusion with St Thomas's solution (30 mmol/l potassium) for 30 minutes, however, abolished the endothelial dependent serotonin induced vasodilatation (serotonin −1·6 (1·43)%, GTN 36·9 (2·2)%. Perfusion with Bretschneider solution (30 mmol/l potassium) gave similar results (serotonin −2·1 (1·23)%, GTN 36·4 (1·65)%).

We conclude that potassium concentration in cardioplegic solutions as used clinically is not detrimental to the endothelium. Increasing the concentration of potassium to 30 mmol/l, however, can cause endothelial damage.

Evidence for a role for nitric oxide in mediating endothelium dependent responses in human epicardial coronary arteries

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Endothelium dependent relaxations have been reported to be mediated through release of nitric oxide (NO) in animal vascular tissue. There has been no direct evidence, however, that NO is the endothelium relaxing factor in human vascular tissue. One hundred and thirty two ring segments of coronary artery were removed from 23 patients undergoing heart transplants for reasons other than ischaemic heart disease. The segments were suspended in 5 ml organ baths for in vitro recording of vascular smooth muscle relaxations. Substance P (SP) (10^{-10}M to 10^{-7}M) elicited a dose dependent relaxation of coronary artery segments. This action of SP is dependent on an intact endothelium. The maximum response of SP was equivalent to 89 (8·5)% of the maximum effect induced by 1 μg/ml glyceryl trinitrate (GTN). The action of SP was unaffected by the presence of 10^{-6}M indomethacin. L-N G-Monomethyl arginine (10^{-4} mol/l), a specific inhibitor of NO formation from L-arginine, antagonised the relaxations induced by SP, decreasing the maximum response of SP to 25 (7·8)% of the response with GTN. On application L-N G-Monomethyl arginine caused a further 29·3 (10·1)% increase in tension on preconstricted vessels, which was reversed with the addition of L-arginine but was unaffected by D-arginine.

It is concluded that the relaxations induced by SP on human epicardial coronary arteries is mediated by an endothelial derived factor, which our data indicate to be NO, cleaved specifically from L-arginine.

Eosinophils from hypereosinophilic patients damage endocardium of isolated heart muscle

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Clinically, hypereosinophilia is associated with endocardial damage to the heart, but a causal relation is not established. We therefore studied the effect of eosinophil suspensions (containing 38–80% "hypodense"—that is, activated—eosinophils) or eosinophil supernatants from eight untreated hypereosinophilic patients on contraction of isolated cat cardiac papillary muscle preparations (n = 16). Eosinophil suspensions (5–15 × 10^6/10 ml tissue bath) or supernatants (prepared by overnight incubation of eosinophils at 37°C) induced within 30 minutes contractile changes identical to the previously reported and characteristic effects of selective endocardial damage—that is, reduced time to peak isometric tension (−6·6%, $p < 0{\cdot}05$) and isometric tension (−8·6%, $p < 0{\cdot}05$) but unchanged unloaded shortening velocity. Light and electron microscopic studies showed a specific pattern of damage to endocardial cells but an undamaged myocardium. Neither the eosinophils nor their supernatants induced any change in contraction of muscles denuded of endocardium (n = 3). Similarly prepared suspensions of eosinophils (containing no hypodense cells) or neutrophils from healthy volunteers caused no contractile or morphological changes in muscles with intact endocardium (n = 10).

Thus eosinophils from hypereosinophilic patients induce morphological and contractile changes in cat papillary muscles suggestive of a pathophysiological role in vivo mediated by endocardial damage.

Increased cough reflex in chronic heart failure independent of treatment with angiotensin converting enzyme inhibitor

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Dry non-productive cough is described as a symptom of chronic left heart failure (CHF). Cough is also a recognised side effect of treatment with angiotensin converting enzyme (ACE) inhibitor, and ACE inhibitors cause increased cough sensitivity to inhaled irritants, but cough reflex has not been studied in CHF. Bronchial hyperreactivity (increased bronchoconstriction to inhaled methacholine) has been reported in subjects with CHF not receiving ACE inhibitors, suggesting that airway abnormalities may be important. The cough response to inhalation of metered doses of α-capsaicin was studied in 10 patients with CHF not receiving ACE inhibitors and in 10 age matched controls. Subjects with CHF were aged 47–76, New York Heart Association grade II or III, and left ventricular ejection fraction was $<45\%$. There was no history of pulmonary disease or atopy, and lung function (forced expiratory volume in one second, forced vital capacity, diffusing capacity for lung carbon monoxide, K_{co}) was $\geqslant 70\%$ of predicted normal values. Deep inspiration through a mouthpiece actuated the delivery of 6·25 nmol nebulised capsaicin in saline (0·02 ml, mass median diameter 4 μm). The number of distinct coughs was noted, and each subject was tested four times in succession on the same occasion. The mean number of coughs in subjects with CHF ranged from 3·5 to 10 (median 6·1) and in controls from 0 to 5·75 (3·9) ($p < 0{\cdot}01$, two tailed Mann-Whitney test).

Increased cough reflex to inhaled irritants in CHF per se may reflect abnormal sensitisation of pulmonary airway receptors, which may contribute to the symptoms of this condition.

Systolic retrograde pulmonary venous flow as a new quantifiable index of mitral regurgitation

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Non-invasive quantification of mitral regurgitation (MR) by ultrasonography is difficult because many technical factors and haemodynamic variables influence the related area of turbulence detected on colour flow mapping (CFM). The most common index of severity—turbulent jet area measured as a proportion of left atrial cross sectional area—cannot usually be obtained by transoesophageal echocardiography (TEE), and it is unreliable in patients with very eccentric MR jets. These confounding factors do not, however, affect left atrial pressure events, which are the major determinants of pulmonary venous blood flow (PVF). As spectral Doppler recordings of PVF are readily obtained by TEE we investigated whether PVF Doppler velocity profiles can be used to measure MR. Pulsed Doppler recordings from the left upper pulmonary vein (LUPV), which is well aligned for Doppler studies, were obtained in 18 adult patients before and immediately after mitral valve reconstruction or mitral valve replacement for isolated angiographic grade III or IV regurgitation. The velocity profiles were digitised with a newly developed microcomputer programme, and the results were compared with conventional ultrasonographic indices of MR such as CFM jet width, depth, and area and the duration of regurgitation on the colour M mode recording. Before surgery 15 patients (83%), including all those with prolapse and an eccentric jet, had abnormal retrograde PVF during ventricular systole. No retrograde PVF was seen in three patients with an early systolic, central MR jet. The time velocity integral (TVI) of the velocity profile was 0·9 (SE 1·7) cm in systole and 8·2 (0·8) cm in diastole ($p < 0{\cdot}01$). After surgery no patient had significant residual MR on CFM as judged by TEE. In five patients MR in early systole (colour M mode) was associated with minimal residual retrograde PVF flow. TVI in systole had increased to 8·7 (0·9) cm ($p < 0{\cdot}05$) whereas TVI in diastole was unaltered, at 7·5 (1·0). The ratio of peak diastolic to peak systolic velocities was 0·55 (0·45) before surgery and 0·97 (0·13) afterwards (NS). Changes in PVF Doppler profiles correlated well with other indices and were helpful in assessing the outcome of surgery.

In conclusion severe MR causes systolic retrograde flow in the pulmonary veins, which resolves immediately after successful surgical repair. TEE analysis of PVF with calculation of systolic TVI seems to be a useful index of the severity of MR.

Echocardiographic assessment of mitral valve repair

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We report our initial experience with conservative mitral surgery since 1985. Fifty eight patients underwent mitral valve repair for mitral regurgitation (MR); 41 were men and 17 women, aged 48 to 79. Follow up ranged from two weeks to four years. One patient was lost to follow up. MR was graded preoperatively by pulsed wave Doppler echocardiographic mapping. Preoperatively MR was moderate-severe and severe in 50 (86%). Seventy eight percent were in New York Heart Association (NYHA) functional class III-IV. In 42 patients MR was due to degenerative changes, in four to ischaemia, seven to rheumatic fever; one had congenital disease, one functional, and two had endocarditis. All but one patient had an annuloplasty ring inserted. Concomitant cardiac procedures included coronary artery bypass grafting (12), aortic valve replacement (seven), patch atrial septal defect repair (one), tricuspid valvotomy (one), and tricuspid annuloplasty (one). There were two deaths at four months after repair, which were unrelated to mitral valve repair. One patient required valve replacement. At follow up 95% of patients were in NYHA class I–II. MR was absent or mild in 52 (90%). Early and late postoperative ultrasonography showed that the septal movement was impaired in all but two patients, with abnormal or paradoxical motion. This is unexplained but limited the echocardiographic measurement of left ventricular function. Function of other myocardial regions seemed to be unimpaired.

This initial satisfactory experience has led to earlier and increased referral of patients with MR for surgical treatment.

Does blood pressure response to the first dose of captopril predict response to subsequent doses in chronic heart failure?

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Captopril (CPT) is used increasingly in chronic heart failure (CHF), and it is common to start treatment with a low dose (6·25 mg). It remains uncertain whether a low starting dose is really necessary, and, furthermore, there is a paucity of data on the blood pressure (BP) response to subsequent doses. The aims of our study were twofold: firstly, to determine whether the first dose effect is different when different starting doses of CPT are given and, secondly, to determine whether the first dose response predicts the response to subsequent doses of CPT. Forty patients with stable, diuretic controlled CHF were recruited into a double blind placebo controlled study comparing either a high dose (25 mg eight hourly for four doses) or a low dose (6·25, 6·25, 12·5, and 25 mg) regimen. No patients withdrew from the study or complained of dizziness or hypotension. Mean BP fell significantly in both groups after the first dose of CPT. In the low dose group mean BP fell by 7 (4) mm Hg after placebo, 16 (4) mm Hg after 6·25 mg CPT, and 18 (4) mm Hg after 25 mg CPT (fourth dose). In the high dose group BP fell by 10 (4) mm Hg after placebo, 15 (4) mm Hg after 25 mg CPT, and 7 (4) mm Hg after CPT 25 mg (fourth dose). The maximum fall in BP after the first dose of CPT was significantly correlated with the fall in BP after the fourth dose in both groups ($r = 0\cdot51$, $p < 0\cdot02$; $r = 0\cdot58$, $p < 0\cdot01$).

These results suggest that the fall in BP after the first dose of CPT is of the same magnitude and duration for either 6·25 mg or 25 mg of the drug. Furthermore the fall in BP to the fourth dose (25 mg) of CPT correlated significantly with that in the first and was in most cases of a lesser magnitude than the response to the first dose.

Hypotension after captopril occurs independently of plasma renin activity and sympathetic nervous activity in patients with primary autonomic failure

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We investigated the haemodynamic and hormonal responses to inhibition of angiotensin converting enzyme in 12 patients with primary autonomic failure (AF) (five with pure autonomic failure and seven with multiple system atrophy) and seven normal subjects. Measurements of blood pressure (BP), heart rate (HR) (Sentron), stroke distance (SD) and cardiac index (CI) (by continuous wave Doppler), forearm blood flow (FBF) (by strain gauge plethysmography), and digital skin blood flow (DSBF) (by laser Doppler flowmetry) were made non-invasively. Plasma renin activity (PRA) (determined by radioimmunoassay) and noradrenaline (NORAD) determined by high performance liquid chromatography were measured before captopril (50 mg oral) and at 30 minute intervals after. Basal supine BP was higher in AF compared with that in normal subjects ($p < 0\cdot05$). After captopril mean BP fell in AF (117 (6) to 103 (5) mm Hg, $p < 0\cdot05$) but not in normal subjects (99 (4) to 97 mm Hg, NS). HR was unchanged after captopril in both groups. The depressor response in AF was accompanied by a fall in SD (9·6 (1·2) to 7·6 (0·7) cm, $p < 0\cdot05$) and in CI (676 (79) to 536 (65) cm/minute, $p < 0\cdot05$). SD and CI were unchanged after captopril in normal subjects (SD 7·7 (1·3) to 7·4 (0·6) cm; CI 579 (117) to 571 (69) cm/minute, both NS). There was no reduction in forearm or digital skin vascular resistance after captopril in either group. Basal PRA in AF was similar to that in normal subjects but did not rise after captopril (691 (217) to 681 (221) pg/ml/h, NS), unlike in normal subjects (813 (103) to 1360 (290) pg/ml/h, $p < 0\cdot05$). NORAD was unchanged after captopril in both groups.

We conclude that captopril lowers blood pressure in AF, unlike in normal subjects. The depressor response in AF occurs independently of renin levels and sympathetic nervous activity, suggesting that alternative mechanisms, including accumulation of bradykinin and prostaglandins are responsible.

Acute β blockade decreases cardiac noradrenaline spillover

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Cardiac and whole blood noradrenaline (NA) kinetics were used to assess the effect of short term administration of metoprolol on cardiac and overall sympathetic activity at rest and during dynamic exercise in 12 patients (mean age 58 (SD 3)) who had not received β blockers for at least seven days. Two periods of supine bicycle exercise were undertaken during infusions of either saline or metoprolol (10–15 mg bolus plus 150 μg/minute intravenously), and NA kinetics were measured before and during each period of exercise. During infusion of metoprolol heart rate decreased from 68 (5) to 61 (5) beats/min ($p < 0\cdot01$) and coronary sinus (CS) plasma flow from 50 (5) to 37 (4) ml/minute ($p < 0\cdot001$). CS NA (171 (21) *v* 141 (15) pg/ml) and arterial NA (171 (15) *v* 158 (16) pg/ml) both tended to decrease, and cardiac NA spillover was significantly decreased during metoprolol (5·6 (0·8) to 3·4 (0·7) ng/minute, $p < 0{\cdot}05$). Whole body NA spillover also tended to decrease during metoprolol (196 (23) *v* 172 (19) ng/minute/m^2). Exercise resulted in increases in CS plasma flow, arterial NA, CS NA, and cardiac NA spillover during both placebo and metoprolol infusions. CS plasma flow during exercise was higher during infusions with placebo than with metoprolol (69 (6) *v* 52 (4) ml/minute), but cardiac and whole body NA spillover were not significantly different. Thus short term administration of metoprolol was associated with a striking decrease in resting coronary blood flow, attenuation of the increase in coronary flow with exercise, and a modest decrease in resting cardiac NA spillover.

The results suggest that, in addition to blocking cardiac postsynaptic receptors, β_1 selective adrenoceptor antagonists may decrease NA release from the cardiac sympathetic nerves.

Comparative study of the efficacy and safety of sotalol in prophylactic treatment of patients with paroxysmal supraventricular tachycardia

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One hundred and twenty six patients were entered into a randomised double blind placebo controlled multicentre parallel group comparison study to assess the relative efficacy of placebo versus sotalol 80 mg twice daily versus 160 mg twice daily in the management of paroxysmal supraventricular tachycardia (PSVT), including atrial fibrillation (AF), atrial flutter, atrioventricular re-entrant (AVRT), atrioventricular nodo-re-entrant (AVNRT), and paroxysmal atrial tachycardia (PAT). The frequency of episodes of PSVT was monitored during three baseline periods, the length of which were related to the frequency of symptoms and which could be one, two, or four weeks. There followed a one week dose escalation period in three parallel groups of placebo ($n = 45$), sotalol 80 mg twice daily ($n = 35$), and sotalol 80 mg twice daily ($n = 46$) increasing to 160 mg twice daily ($n = 44$). During the double blind phase PSVT events and symptoms were monitored as in the baseline phase using diary cards and "Cardiomemo" solid state recorders. The relative risk (Cox's proportion of hazard) of a recurrence of PSVT detected by electrocardiography (ECG) in the 95 patients completing the study was less in the treatment group ($p = 0{\cdot}042$, $p = 0{\cdot}0009$) with 80 mg and 160 mg respectively. After excluding 15 patients (four taking placebo, five 80 mg sotalol, and six 160 mg sotalol) without recurrence of PSVT on ECG or whose period in the double blind phase was too short according to the protocol 80 patients remained. Five of 26 (19%) of patients taking placebo, 11/23 (48%) taking 80 mg sotalol, 21/31 (68%) taking 160 mg sotalol experienced no recurrence of PSVT ($p = 0{\cdot}018$, $p = 0{\cdot}0002$ respectively by logistic regression). Subgroup analysis showed that sotalol was effective in suppressing attacks of PAF at both 80 mg and 160 mg twice daily ($p = 0{\cdot}017$, $p = 0{\cdot}003$ respectively (Fisher's exact test) but of AVRT or AVNRT only at the higher dose ($p = 0{\cdot}683$, $p = 0{\cdot}032$ respectively (Fisher's exact test). No significant unwanted effects were observed.

It is considered that sotalol is a useful and safe product in the management of PSVT.

Effects of theophylline, atenolol, and their combination on myocardial ischaemia in patients with stable angina pectoris

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The effects of theophylline (400 mg twice a day), atenolol (50 mg twice a day), and their combination on myocardial ischaemia were studied in nine patients with stable angina in a randomised, single blind, triple crossover trial. Placebo was given to the patients during the run in and run off periods. A treadmill exercise test and 24 hour Holter monitoring were obtained at the end of each treatment period. Compared with placebo theophylline improved the time to the onset of myocardial ischaemia (1 mm ST segment depression) from 7·8 (3·7) to 9·5 (3·7) minutes ($p < 0{\cdot}03$) and the exercise duration from 9 (3·4) to 10·1 (3·5) minutes ($p < 0{\cdot}04$). During atenolol treatment and combination treatment the time to the onset of ischaemia and the exercise duration were similar (10·8 (4·2), 11·2 (3·2) minutes and 11·2 (3·6), 11·5 (3·2) minutes respectively) and longer than during theophylline ($p < 0{\cdot}05$). Holter monitoring showed that during theophylline treatment the heart rate was higher than during placebo treatment throughout the 24 hours ($p < 0{\cdot}05$). During atenolol treatment and combination treatment the heart rate was similar and in both cases lower than during placebo treatment ($p < 0{\cdot}05$). Compared with placebo theophylline decreased the total ischaemic time from 97 (110) to 70 (103) minutes ($p < 0{\cdot}05$). During combination treatment the total ischaemic time (5·6 (8·5) minutes) was not statistically different from that during atenolol administration (18 (29) minutes), although it was significantly lower than that observed during theophylline treatment ($p < 0{\cdot}05$).

Thus long term theophylline administration improves myocardial ischaemia but to a lesser degree than atenolol. The apparent lack of detectable additive effects, despite the fact that atenolol abolishes the undesirable chronotropic effect of theophylline and that theophylline probably reduces the undesirable increase of cardiac volumes caused by atenolol, suggests that these two drugs might share a common mechanism of action.

Rotational angioplasty for chronic coronary occlusions

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A new rotational angioplasty catheter system (ROTACS) has been developed at Frankfurt for use in chronic coronary occlusion. It consists of a smooth olive shaped tip with an oval cross section attached to a helical drive shaft that rotates at up to 300 rpm and is enclosed in a 5F catheter. Through the centre runs a hole large enough to take a standard (0·014) angioplasty guide wire. We have used the ROTACS in four patients. Patient 1 (aged 67) had previous coronary artery bypass graft (CABG) with a failed left anterior descending (LAD) artery graft. The LAD lesion was a chronic (three years) calcified, but subtotal occlusion, which was successfully passed by the guide wire, opened by the drill, and dilated with a 2·5 mm balloon. Patients 2, 3, and 4 (aged 59, 52, and 67 respectively) all had chronic total occlusions of the circumflex artery and all underwent unsuccessful attempts to cross with conventional percutaneous transluminal coronary angioplasty systems. In patient 2 attempts to cross with the ROTACS were abandoned after the drive seized on to the guide wire. In patient 3 also the drive seized after some progress had been achieved, but a second device was used successfully. In patient 4 the occlusion was crossed and dilated without trouble. There were no complications. Patient 2 was referred for single vessel CABG; the other three procedures were angiographically and clinically successful.

We conclude that the ROTACS technique is not without technical difficulties but widens the scope for non-surgical intervention in coronary disease.

Silent myocardial ischaemia before and after coronary artery angioplasty in patients with stable and unstable angina

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Ambulatory ST segment monitoring was carried out in a series of 69 patients with stable (35) and unstable (34) angina pectoris undergoing successful, uncomplicated coronary artery angioplasty. The frequency, duration, and severity of ST segment depression was analysed to determine its relation to several angiographic features. Patients were monitored for 24 hours immediately before, after, and between 48–96 hours after angioplasty. All episodes of ST segment depression recorded were asymptomatic. Before angioplasty ST depression was seen in 12/35 (34%) of stable and 14/34 (44%) of unstable patients (NS). Immediately after angioplasty ST segment depression was still frequent in 8 (22%) and 11 (32%) of stable and unstable patients respectively. The mean duration and extent of ST segment depression was 38·9 minutes and 1·8 mm in the stable group and 26·2 minutes and 1·3 mm in the unstable group before dilatation. After angioplasty it was 92·4 minutes and 3·1 mm in the stable group and 192 minutes and 1 3 mm in the unstable group. At 48–96 hours after angioplasty ST segment depression was present in nine and six patients in the stable and unstable groups respectively. There was no association between the occurrence of ST segment depression at any time period and angiographic features.

Silent ST segment depression is a frequent finding in patients with both stable and unstable angina undergoing coronary artery angioplasty. The frequency of ST depression decreases after successful angioplasty ($p < 0{\cdot}05$), but the duration and severity of ST depression is increased.

Urgent general practitioner referral to a cardiac centre: evaluation of a chest pain clinic

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In patients with chest pain of recent onset the value of an electrocardiographic reporting service is questionable, and full assessment may be preferred. Therefore after the introduction of an acute chest pain referral service 154 patients, referred by their general practitioners over a year, were reviewed. They comprised 105 men and 49 women (mean age 59, range 25 to 84). The mean duration of symptoms was 19 days (range one to 90 days), and all patients were seen within one day after referral. One hundred and eleven patients (72%) were assessed within one month after the onset of symptoms, and 59 (38%) were seen within seven days. The clinical diagnosis was of unstable angina in 37 patients (24%) and stable angina in 48 (31%). Four patients (3%) had acute infarction whereas 48 (31%) were considered to have non-cardiac pain. In 17 patients (11%) the cause of chest pain was uncertain. The resting electrocardiogram was normal in 83 patients, including 12 considered to have unstable angina. Thirty seven patients were admitted directly from the clinic; 73 patients (47%) underwent coronary arteriography, of whom 32 (44%), in whom the initial electrocardiogram was normal in 13, were investigated within one month. Of all patients investigated, 45 (62%) underwent intervention (percutaneous transluminal coronary angioplasty (23) and coronary artery surgery (22)), 16 within one month of presentation.

An electrocardiographic reporting system is not in itself enough to evaluate chest pain properly. This experience underlines the value, and illustrates the effect on facilities for early investigation and intervention, of a service offering a full assessment of patients with chest pain of recent onset.

How quickly is defibrillation performed in coronary care and other medical wards?

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When ventricular fibrillation occurs outside hospital response time is of major importance, but little accurate information is available on the timing of defibrillation in hospital. Response time (from cardiac arrest call to first defibrillation) was accurately measured in coronary care units (CCU) and medical wards. The precise time of the arrest call was recorded automatically by the hospital switchboard. Each defibrillator carried a modified tracker recorder, which recorded cardiac rhythm, elapsing time, and defibrillation markers automatically. No patient was further than 50 m from a defibrillator. In a year 66 fibrillation arrests (34 in CCU) were recorded in 48 patients; 19 patients survived to leave hospital. Response time <3 minutes was associated with improved survival (52% *v* 8%). Arrests in CCU were associated with shorter mean response time (35 seconds *v* 202 seconds) and improved survival (68% *v* 29%). In the medical wards mean time from arrest call to monitor connection was 125 seconds, and fibrillation was displayed for more than one minute before any defibrillation in 19 out of 32 arrests (maximum 235 seconds). Response times were not significantly longer at night.

Defibrillation outside CCU could be speeded up by obtaining the defibrillator more quickly and training nursing staff to use it.

Heart failure in a district general hospital

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The management of heart failure is an important consideration in allocating resources in a district general hospital

(DGH). This study reports the proportion of patients entering our hospital as medical admissions who have heart failure, the investigatory techniques used to establish the diagnosis and aetiology, the accuracy of diagnostic codes assigned to the patients, and patient outcome. The hospital, in north west London, serves a population of 155 000. The total number of admissions to the medical and geriatric wards during six months was obtained by adding together deaths and discharges. The number of patients with heart failure was determined by a prospective weekly ward survey and a retrospective study of all patient records with diagnostic codes for heart failure or pulmonary oedema. During the six months 2877 patients were admitted to the two services, of whom 140 (4·9%) had heart failure. Only 69 of these patients had been assigned appropriate diagnostic codes. There were 71 males and 69 females; only 29 patients were aged under 65. An electrocardiogram was done in 137 patients; 48 of these showed atrial fibrillation. Chest radiography was done in 136 patients; 86 films showed pulmonary oedema. Only 81 patients underwent echocardiography. The aetiology of heart failure was considered to be: coronary artery disease (41%), valve disease (9%), hypertension (6%), cor pulmonale (4%), a dilated cardiomyopathy (1%), congenital heart disease (1%), thyrotoxicosis (1%), and unknown (36%). The mean duration of hospital stay was 16·7 (16.7) days. During the period of hospital stay 42 patients (30%) died; a further 20 (14%) died during a one year follow up.

In a DGH heart failure is a common reason for admission, the population affected is elderly, and the prognosis is poor. Essential diagnostic techniques are not being carried out in a significant proportion of patients. The accuracy of diagnostic coding must be questioned.

Blood velocity fields at arterial bifurcations: in vivo measurement by high frequency pulsed Doppler velocimetry

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Endothelial function depends on patterns of shear stress, intimately related to the blood velocity field. As this may be important in atherogenesis, which occurs preferentially at bifurcations, we measured velocity fields around eight surgically exposed canine iliofemoral bifurcations with 20 MHz 80 channel Doppler velocimetry. Peak Reynold's numbers ranged from 196 to 564 and frequency parameters from 2 to 4·1, suggesting flow with both viscous and inertial effects important. Geometry was assessed by casts, photography, and 25 MHz ultrasound imaging. The bifurcations were planar to within 5° and asymmetrical; vessel diameters were 3·2 (0·9) mm upstream; 3·4 (1·1) mm and 1·8 (0·4) mm downstream, and bifurcation angles were 58 (10°). Differences in measured velocities among dogs were unrelated to geometrical differences or flow distribution between daughter vessels, which was altered by variable rate pacing. Strong secondary flows were detected, and three dimensional velocity fields were reconstructed from measured vectors. The secondary flows caused profiles calculated on the assumption of parallel flow to be misleading.

The measured velocities indicated spatial differences in shear stress that may explain regional variations in endothelial function and plaque formation at bifurcations.

Effect of two laser and dynamic angioplasty devices on platelet reactivity

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Dynamic and laser atherectomy devices are being assessed for coronary angioplasty. Their interaction with arterial wall is the focus of many studies. Their effects on blood elements, however, are largely unknown. We investigated the influence of a dynamic angioplasty catheter with a fast rotating tip "Kensey catheter" (KC) and continuous wave neodymium-yttrium aluminimum garnet (Nd-YAG) (1604 nm) laser (with sapphire tip) on in vitro platelet function. Blood from healthy volunteers was citrated and divided into 5 ml samples of whole blood (WB) or platelet rich plasma (PRP). These were exposed to Nd-YAG laser pulses of 10, 25, 50, or 100 J. Similar samples were exposed to the dynamic catheter rotating at 20, 40, or 80 thousand rpm. Control samples were exposed to the appropriate device without activation. Platelet count (PC), platelet aggregate ratio (PAR), and extent of platelet aggregation to collagen in WB and PRP were measured and compared with values in control samples. The KC caused inhibition of platelet aggregation in WB and PRP proportional to speed and duration ($r = 0.81$, $p < 0.001$). A similar effect was obtained with laser energies >10 J ($r = 0.69$, $p < 0.001$); lower energies potentiated aggregation ($p < 0.01$). There was no change in PC or PAR to account for either phenomenon. Transmission electron microscopy showed no appreciable membrane disruption of platelets or release of granules.

Exposure to these angioplasty devices inhibits in vitro platelet function without apparent loss of the integrity of platelet structure. This phenomenon and its clinical implication for coronary angioplasty using these techniques justify further study.

Central modulation of dyspnoea in chronic heart failure related to opioid axis

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The pathophysiological mechanisms of dyspnoea in chronic left heart failure (CHF) are poorly understood. The level of dyspnoea correlates only weakly with cardiac function and central haemodynamics. The perception of dyspnoea may involve similar mechanisms to the perception of pain: central modulation could explain differences in the severity of dyspnoea between individual patients and in the same patient at different times. The relation between exertional dyspnoea and pain threshold was studied in 40 patients with CHF, New York Heart Association (NYHA) grade II-III. Dyspnoea was assessed with visual analogue scales during maximal symptom limited treadmill exercise, and exercise capacity was measured as peak oxygen consumption ($\dot{V}O_2$max). The effects of modulating the opioid axis were studied in 10 subjects with NYHA grade III CHF with dihydrocodeine 1 mg/kg and naloxone 0·5 mg/kg. The threshold times for cold immersion pain and for forearm ischaemic pain both correlated with indices of dyspnoea ($r = -0.41$, $p < 0.01$; $r = -0.37$, $p < 0.02$). Dihydrocodeine increased $\dot{V}O_2$max by 14% ($p < 0.05$) and reduced dyspnoea at a standard workload by 19%

($p < 0{\cdot}02$). Naloxone slightly reduced $\dot{V}O_2$max by 8% ($p < 0{\cdot}05$) and increased dyspnoea at a standard workload by 16% ($p < 0{\cdot}02$).

These data suggest that the sensation of dyspnoea can be effectively modulated by centrally acting drugs. This offers the possibility of symptomatic drug treatment of dyspnoea in CHF and provides an insight into the central mechanisms modulating the perception of dyspnoea.

Ion exchange across inactive skeletal muscle during exercise in heart failure

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The participation of non-exercising skeletal muscle in the modulation of exercise induced ionic and acid-base changes was assessed in seven patients with severe heart failure. The changes in plasma potassium (K^+), hydrogen ion (H^+), and lactate (La^-) concentrations and carbon dioxide tension (pCO_2) across inactive forearm muscle were measured during and after bicycle exercise (workload 64 (19) W, peak oxygen consumption 10·5 (2·8) ml/kg/minute) in seven patients with heart failure due to ischaemic heart disease ($n = 4$), dilated cardiomyopathy ($n = 2$), or valve disease ($n = 1$). Arterial and deep venous forearm blood was sampled at rest, at peak exercise, and at two, five, seven, and 10 minutes after. Mean arterial K^+ concentrations rose by 0·57 (0·24) mmol/l ($p < 0{\cdot}01$) at peak exercise but returned to baseline within two minutes whereas venous potassium concentration was unchanged. Arteriovenous K^+ difference thus increased from 0·07 (0·06) to 0·57 (0·46) ($p < 0{\cdot}05$). Mean H^+ concentration and pCO_2 increased across inactive forearm muscle by 5·3 (2·3) nmol/l ($p < 0{\cdot}01$) and 1·48 (0·3) kPa ($p < 0{\cdot}01$) respectively during exercise, and these changes persisted for five minutes after exercise. Arterial La^- concentration rose from 1·45 (0·36) to 3·18 (1·12) mmol/l at peak exercise and 4·74 (2·18) at five minutes after exercise (both $p < 0{\cdot}01$). Arteriovenous La^- difference increased from −0·31 (0·26) to 0·6 (1·25) mmol/l ($p < 0{\cdot}05$).

These data show that uptake of K^+ and La^- by inactive skeletal muscle occurs during exercise in patients with heart failure and indicate that inactive muscle may be involved in H^+ homoeostasis.

Enoximone in patients with severe heart failure who continue to have symptoms despite treatment with angiotensin converting enzyme inhibitors and diuretics

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In patients with chronic heart failure who have symptoms despite treatment with angiotensin converting enzyme inhibitors, drugs that cause further vasodilatation may be beneficial. Enoximone relaxes vascular smooth muscle by increasing cyclic adenosine monophosphate concentrations. Ten patients, all taking diuretics and captopril, completed a double blind, placebo controlled study to evaluate the addition of four weeks of enoximone. Exercise capability was measured with two treadmill tests, an incremental and a fixed workload protocol, and a corridor walk test and by step counting with pedometers. Cardiac output was measured with an indirect Fick method and limb blood flow by venous occlusion plethysmography. Enoximone increased exercise time with the incremental test from 498 (91) to 573 (94) seconds after two weeks ($p = 0{\cdot}051$) and to 572 (100) seconds after four weeks ($p = 0{\cdot}057$). With the fixed test exercise duration increased from 252 (75) to 431 (98) seconds after two weeks ($p = 0{\cdot}011$) and to 381 (85) seconds after four weeks ($p = 0{\cdot}01$). The improvement with the fixed test was greater than that with the incremental protocol at weeks 2 and 4 ($p = 0{\cdot}01$, $p = 0{\cdot}037$). It improved the corridor walk test but had no effect on pedometer scores. It increased cardiac output during exercise ($p = 0{\cdot}01$) and blood flow to the calf, and therefore to skeletal muscle, at rest and after exercise ($p = 0{\cdot}01$).

Enoximone improves the exercise capability and haemodynamic variables in patients who have not responded adequately to diuretics and captopril. The magnitude of the effect depends upon the technique used to assess it.

Lignocaine aerosol anaesthesia and dyspnoea in chronic left heart failure

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Stimulation of J receptors and other intrapulmonary receptors has been postulated as the cause of dyspnoea in chronic left heart failure. We assessed the role of these receptors by observing the effects of inhaled small particle aerosols of local anaesthetic. Ten patients with New York Heart Association grade II–III chronic heart failure (CHF) without evidence of intrinsic pulmonary disease were studied. Aerosol with a mass median diameter of 1 µm was generated, ^{99m}Tc-diethylene triamine pentaacetic acid labelled aerosol was shown to deposit uniformly in the peripheral lung fields with a peripheral penetration index of 0·94 relative to krypton gas. Each subject performed maximal treadmill exercise limited by dyspnoea, once after lignocaine aerosol, and once after isotonic saline aerosol as control, given in random order. Exercise capacity was determined as peak oxygen consumption ($\dot{V}O_2$max) from analysis of mixed expired gases. Lignocaine aerosol abolished the cough response to inhaled capsaicin without producing measurable blood concentrations. Gag reflex and phonation were unchanged. There was a minor (6%) fall in forced expiratory volume in one second after lignocaine aerosol. Exercise $\dot{V}O_2$max after lignocaine aerosol was 10·8–22·2 (median 17·4) ml/kg/minute and after saline aerosol was 10·4–21·1 (17·6) ml/kg/minute. There were no significant differences in respiratory rate, peak ventilation, or visual analogue scores for dyspnoea.

These results suggest that, contrary to expectation, pulmonary airway receptors and J receptors are not major afferent sources for the sensation of dyspnoea in CHF.

Effect of supine posture on lung mechanics in chronic left ventricular failure

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The mechanisms of orthopnoea in heart failure are still not well understood, partly because of difficulty in obtaining reliable measurements of pulmonary mechanics in the supine position. We adapted the forced oscillation technique to measure total respiratory resistance (Rrs) in the sitting and supine positions. Nine patients (8 men, mean age 61·6) with chronic left ventricular failure (New York Heart Association class II–III) and eight matched controls (7 men, mean age 61·5) were studied. Rrs, mid-tidal lung volume (MTLV), spirometry, oxygen saturation (Sao_2) and visual analogue scores for breathlessness (VAS) were recorded in the sitting position, after five minutes' supine rest, and five minutes after return to the sitting position. In the sitting position mean (SE) Rrs in the patients was significantly higher than in controls (3·54 (0·28) *v* 2·35 (0·35) cm H_2O/l/second, $p < 0·05$). Lung volumes were reduced in the patients: total lung capacity (% predicted) was 81·5 *v* 103·9, forced expiratory volume in one second (FEV_1) (% predicted) was 68·3 *v* 106·1, and forced vital capacity (FVC) (% predicted) was 62·3 *v* 97·8 compared with controls (all $p < 0·01$). FEV_1/FVC% was 77·3 in patients *v* 75·9 in controls (NS). Rrs increased significantly more in patients than in controls on lying supine (85·4 (13·0)% *v* 39·1 (13·0)%, $p < 0·01$). Vital capacity declined more in patients than in controls (217 *v* 100 ml, $p < 0·01$). Sao_2 did not change in either group. There was a 79·5% increase in VAS dyspnoea scores in supine compared with sitting patients ($p < 0·05$). No control subjects experienced dyspnoea. On patients resuming the sitting position, all measurements reverted to initial sitting values.

We conclude that patients with chronic left ventricular failure show a substantial reversible increase in airways resistance accompanied by subjective dyspnoea on changing from the sitting to the supine position despite a small decline in MTLV.

Disclosure of increased free radical activity in heart failure by biochemical markers and proton nuclear magnetic resonance spectroscopy

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Free radicals (FRs) can cause myocardial dysfunction. Recurrent episodes of myocardial ischaemia, hypoperfusion-reperfusion cycles in other vascular beds and neuroendocrine activation may lead to increased FR generation in chronic heart failure (CHF). We sought evidence for this in two groups of patients with CHF. Group A (n = 15, age range 30–66) had CHF due to coronary artery disease (CAD); because CAD itself may be associated with increased FR activity a second group (group B), (n = 15, age range 27–79) with CHF and normal coronary arteries (no CAD) was also studied. Both groups had a comparable degree of systolic dysfunction on echocardiography and were similarly treated with diuretics, digoxin, and vasodilators. Lipid peroxides, markers of FR damage to lipids (where peroxides increase), and plasma thiols, markers of damage to proteins (where thiols decrease), were measured in peripheral venous blood. In normal controls (n = 13, age range 23–64) lipid peroxides were 7·6 (6·5–8·3) nmol/ml (median and interquartile range) and thiols 505 (492–509) µm/l. Compared with controls both patient groups showed comparable abnormalities in FR markers: in group A (with CAD) lipid peroxides were 10·0 (8·6–11·0) nmol/ml ($p < 0·01$) and thiols 384 (351–451) µm/l ($p < 0·05$); in group B (non CAD) lipid peroxides were 9·3 (8·85–10·3) nmol/ml and thiols 364 (339–418 µm/l (both $p < 0·01$). In a further group of 10 patients proton nuclear magnetic resonance spectroscopy of erythrocytes showed a significant reduction in the signal for reduced glutathione, an intracellular FR scavenger.

These results show that CHF per se is associated with increased PR activity in humans. It is possible that FRs contribute to myocardial dysfunction in CHF.

Reduced exercise capacity in patients with tricuspid regurgitation after successful mitral valve replacement for rheumatic mitral valve disease

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Impaired exercise capacity after successful mitral valve replacement (MVR) for rheumatic mitral valve disease (MVD) may result from prosthetic valve dysfunction, persistent pulmonary hypertension, or left ventricular dysfunction. This study reports that the late development of tricuspid regurgitation (TR) is also an important cause of impaired exercise capacity. We studied 19 patients who had previously undergone MVR for rheumatic MVD; nine with clinically significant TR and 10 without. The groups were matched for age and sex, preoperative New York Heart Association class, symptom duration, mean pulmonary artery pressure (PAP) and mitral lesion, and for mitral prosthesis. All had normal preoperative left ventricles and coronary arteries and no significant aortic or tricuspid valve lesion. Postoperative prosthetic mitral valve function was normal and systolic PAP and left ventricular function similar in both groups. Subjects were assessed by echocardiography and colour flow Doppler and maximal treadmill exercise; expired gas was monitored by mass spectrometry. Exercise tolerance was impaired in patients with TR: NYHA class (2·8 (0·6) *v* 1·2 (0·4), $p < 0·001$), exercise duration (6·6 (2) *v* 11·3 (3) minutes, $p < 0·001$), and peak oxygen consumption (10·8 (3·2) *v* 16·6 (3) ml/minute/kg, $p < 0·001$). Respiratory exchange ratio at peak exercise was similar (1·02 (0·07) with TR *v* 1·07 (0·07) without), indicating maximal exercise in both groups. Patients with TR had smaller increases in systolic blood pressure at maximal exercise (5 (14) *v* 22 (19) mm Hg, $p < 0·05$), and minute ventilation at the same minute carbon dioxide production was greater in patients with TR (41·9 (7·8) *v* 33·6 (4·2) l/minute, $p < 0·01$).

We conclude that clinically significant TR may develop after successful MVR for rheumatic MVD and have shown that this is associated with appreciable impairment of exercise capacity.

Does spatial orientation of the Björk-Shiley mitral prostheses affect hydraulic performance of the valve?

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We studied the influence of disc orientation in Björk-Shiley mitral prostheses (MVR), on the diastolic Doppler flow characteristics and on the effective orifice area. Cross sectional echocardiographic studies with pulsed and continuous wave Doppler and colour flow imaging were performed in 37 consecutive patients aged 40 to 75 (mean age 57 2). Patients were divided into two groups according to the direction of the diastolic excursion of the disc. In group A (22 patients) the orientation of the disc was anterior, opening towards the ventricular septum whereas in group B (17 patients) it was posterior, opening away from the septum. MVR size (group A 28·6 (1 5) mm *v* group B 29·2 (1·2) mm), left ventricular diastolic dimensions (51 (7·8) *v* 51·5 (7·7) mm), fractional shortening (28·9 (9·9) *v* 29·5 (5·8)) incidence (9/22 *v* 8/17), and severity (0·46 (0·6) *v* 0·59 (0·5) cm^2) of aortic regurgitation were similar in both groups. Group A patients had higher peak transmitral gradients when compared with group B patients (9·8 (4·4) *v* 5·1 (1·3) mm Hg, $p < 0{\cdot}001$). The effective mitral valve orifice area was consistently smaller than that of the manufacturers in both groups (group A 1·41 (0·8) cm^2 *v* group B 1 47 (0·64) cm^2), NS) and did not depend on the size of prosthesis. It was not affected by the presence of aortic regurgitation.

It is concluded that in Björk-Shiley mitral prostheses at rest peak gradients are higher when the disc excursion is anterior, but the effective valve orifice area is similar in both orientations and unaffected by the presence of mild aortic regurgitation.

Abnormal leaflet apposition as a cause of mitral regurgitation: a new finding?

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Both transoesophageal and epicardial echocardiography can show the morphology and function of the mitral valve in much greater detail than is possible with conventional transthoracic ultrasonography. With these techniques in 67 patients with New York Heart Association grade III or IV heart failure who were undergoing mitral valve surgery we performed a detailed sequential analysis of the valve leaflets and the zone of coaptation. Absence of leaflet coaptation was identified as the cause of regurgitation in 30 patients. Eight patients had normal leaflet coaptation and apposition and central regurgitation caused by a dilated annulus. In the other patients ($n = 29$) the leaflets seemed to coapt along the whole closure line, from the anterolateral to the posteromedial commissure, but there were eccentric regurgitant jets related to an asymmetrical overlap of one leaflet above the other—that is, abnormal apposition. These appearances were often mild, being present without echocardiographic criteria diagnostic of leaflet prolapse. This pattern has not previously been widely recognised as a substrate for mitral regurgitation. To study its possible mechanism eight hearts obtained at necropsy from patients who had died from non-cardiac causes were perfused under pressure retrogradely through the aortic valve, to fix the mitral valve leaflets in the closed position, thus simulating systole. The hearts were sectioned, and the minimum dimensions between the free edges of the leaflets and the border of the rough zone, corresponding to the width of normal leaflet apposition, were measured. The minimum dimension at any site along either leaflet was 1·5–4·0 mm (mean 2 9 mm).

These data suggest that asymmetrical apposition of the mitral leaflets, in which one leaflet protrudes towards the left atrium by 3 mm or more over the other leaflet at the zone of coaptation, may be sufficient to cause significant regurgitation. The probable mechanism is regurgitation under the reflected edge of the abnormal leaflet, between adjacent primary chordae tendineae. The identification and localisation of this problem will be of value in understanding the mechanism of regurgitation in particular patients, thereby allowing an appropriate mitral valve repair operation to be performed.

Infective endocarditis: Is it a transoesophageal echocardiographic diagnosis?

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The diagnosis of infective endocarditis (IE) and its major cardiac complications can prove difficult using conventional transthoracic echocardiography (TTE). To assess the role of transoesophageal echocardiography (TOE) we studied 60 consecutive patients with suspected IE by both TTE and TOE. TOE suggested IE in 24 of 27 patients in whom IE was subsequently confirmed. Valves affected included the aortic valve (AV) (seven native, nine prosthetic), mitral valve (MV) (seven native, two prosthetic), tricuspid valve (TV) (one patient), and both a TV and pulmonary valve (PV) (one patient). Vegetations were diagnosed by TOE in 17 patients (and confirmed in all five who subsequently underwent surgery) but in only five patients using TTE. In three patients, all of whom had persistent fever despite appropriate antibiotic treatment, TOE showed cavities consistent with aortic root abscesses; only one was seen with TTE. In another two patients TOE disclosed large cavities around the aortic root but underestimated the anterior extent of these compared with surgical findings. TOE disclosed a small mycotic aneurysm on the anterior MV leaflet in two patients and a fistula in a patient with an aortic root replacement; these had not been detected with TTE. TOE did not suggest IE in any of the 33 patients with other clinical diagnoses. TOE was limited in several respects: (1) the anterior aspect of the aortic root was not well visualised; (2) assessment of prosthetic AVs was limited by acoustic shadowing; and (3) TOE did not provide additional information in the patients with TV and PV IE.

We conclude that TOE provides important anatomical and functional insights in patients with documented IE but should not be used to exclude the diagnosis. Early use of TOE in suspected IE should increase the diagnostic yield and help reduce the morbidity and mortality associated with this serious condition.

Who refers patients for repeat valve operations?

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We have reviewed our experience of patients who required repeat valve replacement over four years, during which 286 tissue valves and 496 mechanical prostheses were inserted in our institution; 48 patients (16%) underwent repeat valve replacement. Of these, 30 patients (62%) had previous tissue valves and 18 (38%) mechanical valves. Repeat valve replacement was necessary because of degeneration of the prosthesis in 22 patients (45%), endocarditis in 14 (29%), paraprosthetic leak in seven (15%), thrombotic occlusion in three (6%), dehiscence of valve ring in one (2%), and haemolysis in one (2%). Eleven patients were admitted with pulmonary oedema, and in only one case was this due to endocarditis. The pattern of re-referral for consideration for further surgery was surprising. Deterioration in the patient's condition was most often detected by the general practitioner despite the fact that all of these patients were under "routine" medical and surgical follow up: 70% were referred back by general practitioners, 4% by cardiac surgeons, and 26% by cardiologists. Even excluding patients who were admitted as emergency cases with suspected endocarditis or jammed prostheses, further assessment for reoperation was initiated by general practitioners in 63% of cases.

These findings raise questions about the merits of hospital follow up of patients with heart valve prostheses.

Value of complete myocardial revascularisation in combined ischaemic and mitral valve surgery

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Operative and follow up data on 70 patients with combined myocardial revascularisation and mitral valve surgery (63 valve replacements, four repairs, and three replacements) were analysed to assess the early and late outcomes. The valve disease was of ischaemic origin (ischaemic heart disease (IHD) group) in 30 patients (43%) and non-ischaemic origin (non-IHD group) in 40 (57%). Thirty patients had surgery between 1977 and 1984 (17 IHD, 13 non-IHD) and 40 between 1985 and 1989 (13 IHD, 27 non-IHD). The operative mortality for the ischaemic group came down between the two periods (from 53% to 15%) and remained similar in the non-ischaemic group (7·6% *v* 11%). Patients with complete myocardial revascularisation had a much lower operative mortality than those with incomplete revascularisation (20% *v* 53%, IHD group; 6·6% *v* 20%, non-IHD group). In the last 40 patients at the end of a mean of 18 months' follow up (range 2–62 months) two thirds of patients in the IHD group and one third of those in the non-IHD group were of New York Heart Association class I–II functional state.

Our results suggest that all patients with mitral valve disease should undergo coronary angiography before valve surgery, and to minimise the operative risk complete myocardial revascularisation is strongly recommended.

Early experience of a low speed drill for recanalisation of chronic total coronary occlusions

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The success rate of conventional angioplasty in chronic coronary artery occlusion is low (<50% and decreasing with age of occlusion). Low speed rotational coronary angioplasty (RA) has been shown to be safe, and primary success rates of up to 60% have been reported. We attempted RA with the rotational angioplasty catheter system (ROTACS) device on six occlusions (five right coronary, one circumflex) in six patients in whom attempts at conventional angioplasty had failed (five unable to pass guide wire; one unable to pass balloon over wire). Estimated duration of occlusion was five to 18 (mean 10) months. Mean length of occlusion was 2·4 (range 0·5–3·2) cm. Successful recanalisation followed by conventional balloon angioplasty was achieved in 2/6 (including the patient with successful passage of the guide wire). Three attempts to recanalise the right coronary artery were unsuccessful. On each occasion the ROTACS drilled along the full length of the occlusion, but it was impossible to pass a guide wire into the distal lumen. Simultaneous contrast angiography of right and left coronary arteries showed the exact position of the drill tip to be within 1 mm of the distal vessel lumen in each case. In the one attempt to recanalise a circumflex artery no progress could be made due to the tortuous nature of the proximal vessel, which prevented drill advancement.

Our experience shows a low success rate with RA when conventional angioplasty has failed. A major problem is failure to enter the distal lumen despite successful progress of the ROTACS past the occlusion.

Angioplasty of totally occluded arteries by a probing catheter

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A 21 mm probing catheter (USCI) was used in nine patients with chronic total coronary artery occlusion. Occlusion was present for five (two) months (range 1 to 10 months) in the left anterior descending artery (five patients), right coronary artery (three) and left circumflex artery (one). In two patients attempts to cross the lesion with a 2 mm low profile balloon and wire had failed. A standard 0·016 wire (USCI) and probing catheter successfully crossed the lesion in 8/9 arteries. After crossing the lesion distal coronary injection through the probing catheter lumen confirmed the presence of the catheters in the true lumen and outlined the distal artery. A probe balloon or low profile balloon was then passed through the inner lumen of the probing catheter and withdrawn to the site of the stenosis. Serial inflations were performed with a 2·5 or 3 mm balloon, or both, leaving a residual stenosis of 28 (18)% stenosis. In two patients further distal stenoses were also dilated. Only one complication was observed—a distal coronary embolus—and no patient developed infarction or required surgery.

The probing catheter facilitates dilatation of chronic totally occluded coronary arteries.

Intracoronary stents for angioplasty of stenoses of saphenous vein aortocoronary bypass grafts

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The success of percutaneous angioplasty of stenoses of saphenous vein aortocoronary bypass grafts is limited by a very high restenosis rate, up to 60% for proximal graft stenoses. We have embarked on a policy of intravascular stent insertion in patients with stenoses of saphenous vein bypass grafts suitable for angioplasty to attempt to reduce the high restenosis rate in such patients. Currently, seven stents have been inserted in five grafts in five patients. The stent used is composed of a stainless steel alloy, has a self expandable wire mesh design, and is deployed using a 5 French delivery system. In each case, the presenting symptom was limiting angina refractory to medical treatment; angiography had shown initial localised graft stenoses of 70% or more. In all patients insertion of either one stent (four patients) or two stents (one) was completed without initial complications and without residual stenosis on angiography. No patient had early or late complications attributable to the procedure: in one, there was a small rise in the cardiac enzymes but follow up ventriculography showed normal left ventricular function. All patients were either symptomless or had minimal symptoms during three to nine months of follow up; all have undergone follow up angiography, and in none of the cases was there restenosis within the stented segment. One patient developed recurrent angina at three months due to a new stenosis in the proximal graft segment; this responded to further stent insertion.

Stent insertion shows promise as an adjunct to percutaneous angioplasty for stenoses of saphenous vein bypass grafts and may become the treatment of choice if these results are confirmed.

Percutaneous angioscopy: from peripheral to coronary arteries

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Unlike angiography, angioscopy allows direct visualisation of arterial lumen. We used high resolution angioscopes percutaneously before and after angioplasty in peripheral and coronary arteries. The angioscopic features were compared with the corresponding angiographic findings. In 14 patients with peripheral vascular disease 10 had total occlusion treated with Kensey atherectomy catheter (KC). In four with stenotic lesions balloon angioplasty was used. With saline flush, good views were obtained in 13/14 arteries before angioplasty and in 10/14 afterwards due to increased blood flow. Angioscopy revealed features often undetected by angiography and was superior in establishing the precise nature of occlusive pathology (thrombotic or atheromatous). KC did not seem to generate any more luminal disruption than conventional balloon. Encouraged by these results, we made 18 attempts ($n = 18$) at percutaneous coronary angioscopy before and after percutaneous transluminal coronary angioplasty (PTCA) in six patients (one left anterior descending and five right coronary arteries), with either a 0·5 mm diameter ($n = 2$) or 1·4 mm diameter ($n = 4$) angioscope, or both ($n = 12$). The angioscopes were introduced through 9 F PTCA Judkins catheters. An intelligible view was possible in 7/10 attempts with the 1·4 mm diameter angioscope but in only 2/8 with the 0·5 mm diameter angioscope. Angina occurred during 3/10 attempts with the 1·4 mm diameter angioscope. The 0·5 mm diameter angioscope induced angina in 5/8; in one, this was associated with demonstrable coronary spasm. No rise in creatine kinase (heart type) activity was observed in any of the patients. After PTCA angioscopy revealed intimal flaps at all PTCA sites visualised, mural thrombus in one, and small dissection in another; neither was obvious on angiography. In one patient clinical and angiographic features suggested thrombotic pathology; angioscopy showed atheromatous occlusion with no thrombus.

In conclusion, angioscopy provides a new perspective towards understanding vascular disease and evaluating new angioplasty techniques. Although coronary angioscopy seems to be feasible and safe, it requires further improvement. The size of the angioscope may be critical.

From peripheral to coronary arteries: analysis of particles resulting from simulated dynamic angioplasty

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The Kensey catheter (KC) utilises a fast rotating cam and high pressure fluid jet to recanalise occluded arteries. We have successfully used 8 F KC in peripheral arteries, a 5 F size is proposed for coronary use. There has been some concern regarding the risk of embolism of particles resulting from this technique. A study was undertaken to investigate these particles and some of the factors that influence their size. Eighty four fresh endarterectomy specimens were inserted in a flow circuit and randomised to undergo a simulated procedure using a 5 F or 8 F KC at a range of predetermined cam speeds (CS) (20 000–80 000 rpm) and flow rates (FLR) (16–60 ml/minute). The collected debris was mounted on slides, and all particles > 4 µm were measured with computerised edge detection technique. Most particles (median 90·8 (SD 3·4)%) were < 35 µm in diameter. In those remaining (9·2 (3·4)%) significant differences were found between the maximum particle size (MPS) in each group (from 170 to 985 µm). Increasing CS independently reduced MPS from 985 to 320 µm ($p < 0.001$). Increasing FLR and reducing catheter size had a smaller but significant effect on reducing MPS ($p < 0.005$ and $p < 0.01$).

In conclusion, although most particles resulting from the use of KC in atheroma were small, a low proportion of larger particles was also detected. Cam speed, flow rate, and catheter size had significant effects on MPS. These results may be particularly important for future use of KC in coronary arteries.

Coronary angioplasty of chronic total occlusions and tortuous vessels

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Percutaneous transluminal coronary angioplasty of chronic total occlusions or tortuous vessels has been attempted using a balloon on a wire dilatation catheter system (Buchbinder-Versiflex) designed so that the distal tip of the wire can be rotated and flexed through a control on the proximal end of the catheter, potentially allowing extra wire tip control. This is combined with a low profile (0·034 inches for the 2·0 mm diameter catheter). In 57 of 925 consecutive angioplasty procedures this system was used, 15 in the left anterior descending, 15 in the circumflex, and 27 in the right coronary arteries. Lesions were classified as total occlusions (TIMI 0 or 1) of duration less than three months (21) or greater than three months (22), distal or difficult access due to tortuosity or acute angulation (eight) or acute occlusions after angioplasty (six). The system was used as first choice in 20 lesions and as either a second or third line system in the remainder. The success rate, defined as crossed, dilated with residual stenosis less than 50%, was 74% compared with an overall success rate of 92%. The success rate was higher in occlusions less than three months' duration (80%) compared with those greater than three months (64%). The system was successful in five lesions considered to be complex owing to severe tortuosity, acute angulation, or their distal nature. Six acute occlusions after angioplasty were successfully crossed when standard systems could not be reintroduced, four with sustained patency. Overall mortality was 0·5%, and two patients proceeded to urgent bypass surgery, all after acute occlusions with another system. The main disadvantages of the system are that it is not exchangeable over a guide wire and that the lesion needs to be recrossed to introduce a larger balloon. There is also no distal port for contrast injection to exclude a false channel, which occurred in three cases.

This system is an important adjunct to conventional "over the wire" or monorail systems. It is suitable as a first line approach to acute or chronic total occlusions and as a second line system for tortuous or angulated vessels not amenable to crossing with a conventional system and for acute occlusions occurring during angioplasty.

Delay to invasive investigation and revascularisation in coronary heart disease in South West Thames: cause for concern?

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The accessibility of invasive investigation and revascularisation procedures to the population of North West Surrey health district in South West Thames region was audited over the 10 years 1979–88. The mean catchment population during the period was 205 000, and cross boundary flow was balanced. Waiting time to investigation/intervention by the regional cardiac centre was compared with that of the private sector. Deaths of patients on the waiting list for investigation/operation were recorded. The regional centre favoured in the first five years was St Thomas's Hospital, Lambeth, and in the second five years St George's Hospital, Tooting. A total of 823 patients aged 34–80 were referred for investigation of ischaemic heart disease (including 15 with concomitant valvar heart disease), 204 to the private sector. After some initial vacillation the mean waiting time for coronary angiography after referral increased from 68·2 (SE 6·85) days (range 23 to 153 days, n = 42) in 1984 to 114·3 (12·1) days (range 22 to >430 days, n = 98) in 1988 in the public sector, but remained unchanged over 10 years in the private sector, at 15·8 (0·16 days (range 1 to 62 days, n = 204). Mean waiting time to elective surgery in the public sector increased from 107 9 (15·4) days (range 12 to 240 days, n = 26) in 1984 to >274·8 (24·2) days (range 22 to >508, n = >60) in 1988, but the waiting time for emergency angiography remained static at 4·7 (0·07) days (range 0 to 24 days, n = 132) over 10 years and for surgery 26 1 (1·02) days (range 0 to >400 days, n = 103). In the private sector the overall waiting time to angiography was 15 8 (0·16) days (range 1 to 62 days, n = 204) and for surgery 22·8 (0·52) (range 2 to 152 days, n = 124), both taken over 10 years. There were 15 cardiac deaths in patients with ischaemic heart disease alone, all of whom were on the public sector routine waiting lists for catheterisation and surgery. This exceeded the overall surgical mortality (1·4%). Fifty three (8·6%) patients on the public sector waiting list for surgery waited for longer than a year and required reinvestigation, 36 in 1987–8.

Prolonged waiting times to investigation and surgery in the public sector reflect underprovision of service which seems to be worsening in South West Thames region. This exposes these patients to unfair and unjustifiable risks in terms of morbidity and mortality.

Changes in practice of cardiopulmonary resuscitation have not affected outcome

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The United Kingdom Resuscitation Council has modified the guidelines for drug usage in patients with asystolic cardiac arrest. Atropine is recommended as the drug of first choice, calcium is no longer recommended, and sodium bicarbonate should be reserved for patients in whom an acidosis had been reported. We audited the asystolic cardiac arrests for 1982 (n = 55), 1986 (n = 67), and 1988 (n = 57) that occurred outside the cardiac care unit (CCU). Atropine use increased, from 29% to 52% to 61% over the six years. Bicarbonate use did not change from 1982 (74%) to 1986 (74%) but fell in 1988 (35%). Calcium use was similar to that of bicarbonate in 1982 (73%) and 1986 (61%) and fell in 1988 (24%). Adrenaline use has remained unchanged at 72%, 63%, and 65% over the same period. Survival from asystolic arrests (hospital discharge) has remained unchanged at 5·4% (1982) *v* 3·0% (1986) *v* 3·5% (1988) (NS). We also audited the total cardiac arrests (not in CCU) for 1982 (n = 120), 1986 (n = 153), and 1988 (n = 150). Of these, 11·6%, 7·2%, and 8% (NS) were discharged from hospital. Drug usage for all arrests for the three respective years were: bicarbonate 67·5%, 71·2%, and 28%; calcium 59·2%, 58·1%, and 16·9%; adrenaline 50 8%, 76·4%, and 44%; atropine 15·8%, 55%, and 51·8%; and lignocaine 13·3%, 35·3%, and 21·9%. Asystole as a primary event in the CCU was uncommon, occurring in 13 of 956 (1·36%) patients with a myocardial infarction between 1986 and 1988. Seven patients had received atropine as the first drug, and six had attempted emergency pacing. No patient survived to be discharged home. Over the same period there were 43 cardiac arrests in CCU due to ventricular fibrillation (VF), 11 patients having had an anterior myocardial infarction and 12 an inferior one. Of those with VF, 67% were discharged from hospital, with 48·8% known to be alive six months subsequently.

Although the United Kingdom Resuscitation Council guidelines for the management of asystole are becoming assimilated by the resuscitation teams, changing drug usage has not affected outcome. This audit also shows that survival from cardiac arrest has remained constant from 1982 to 1988.

Aspects of psychological and social morbidity in patients awaiting coronary artery bypass grafting

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This study was designed to assess aspects of anxiety, depression, and social adjustment in patients awaiting coronary artery surgery. Patients on the waiting list for routine surgery were sent a series of questionnaires designed for this purpose. One hundred and nine questionnaires were sent, and 68 (62%) were returned. Anxiety and depression were assessed with the hospital anxiety and depression (HAD) scale. Social functioning was assessed by means of several nine point rating scales, on which the patients were asked to indicate the extent to which their work, family relationships, social activities, private leisure activities, and home management were impaired. Patients were also asked to indicate their present severity of clinical cardiac symptoms with the New York Heart Association's classification. On the HAD scale 19 (28%) of patients scored in the clinically significant range for anxiety. Time on the waiting list was positively and significantly related to anxiety ($p = 0{\cdot}05$). Thirty two (47%) of patients scored in the clinically significant range for depression. Time on the waiting list was positively and very significantly related to depression ($p = 0{\cdot}005$). Positive and significant relations were found between time on the waiting list and impairment of work ($p < 0{\cdot}0001$), family relationships ($p < 0{\cdot}0001$), private leisure activities ($p < 0{\cdot}0001$), and social activities ($p = 0{\cdot}004$). No relation was found between any of the above variables and severity of clinical symptoms.

This study highlights the social and psychological consequences of the long waiting lists for coronary artery bypass grafting in this country.

Heartstart Scotland: initial experience of a nationwide scheme for out of hospital defibrillation by ambulance crews

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Widespread provision of out of hospital defibrillation in Britain has been limited by the rate at which ambulance crews can undergo extended training, including tuition, in recognition of electrocardiograms. We attempted an alternative approach in the Scottish Ambulance Service, training ambulance crews in basic life support and in the use of a semiautomatic defibrillator (Laerdal 2000). Between 1 October 1988 and 30 September 1989, 96% of the 2000 vehicle crews completed an eight hour training programme. A total of 268 defibrillators were purchased by public subscription during the study period, resulting in a cumulative availability of 5548 defibrillator weeks. During this period crews equipped with defibrillators recorded data on 1111 cardiac arrests, in which defibrillation was undertaken in 602 (54%). Data on outcome were obtained for all 602 patients from the receiving hospital; 180 patients (29·9%) reached hospital with a spontaneous pulse, and 75 (12·5%) were discharged alive. Extrapolation to the Scottish Ambulance Service's total of 395 ambulances would yield a hospital discharge rate of 278 a year.

Pre-hospital defibrillation with semiautomatic defibrillators is feasible and can be introduced rapidly owing to the limited staff training requirements.

Interpretation of electrocardiograms in the accident and emergency department

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To determine the accuracy with which casualty officers interpret electrocardiograms (ECGs) in patients presenting to the accident and emergency department with anterior chest pain we conducted a prospective double blind study in which casualty officers' interpretation of electrocardiograms was compared with that of a consultant cardiologist. Three hundred and fourteen consecutive patients attending the department with anterior chest pain over a two month period were studied with respect to the percentage of attenders who complained of anterior chest pain, the accuracy with which the casualty officers interpreted normal and abnormal ECGs, and the rate of inappropriate management. Of all those attending the accident and emergency department, 4% presented with chest pain; 90% of normal ECGs were correctly interpreted by casualty officers and 43% of abnormal ECGs were incorrectly interpreted by casualty officers; and 96·5% of patients with chest pain were managed correctly in casualty.

Senior house officers in the accident and emergency department, although good at identifying the presence of an abnormality of an ECG, are less good at defining the nature of the abnormality. This may result in inappropriate management of some patients. Audit of all ECGs should be undertaken by someone with experience of their interpretation. New accident and emergency staff should receive training in the interpretation of ECGs.

Invasive cardiological assessment and intervention: an audit of health district activity

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The requirement for invasive cardiological assessment and intervention in a defined health district in South West Thames region was studied prospectively over the 10 years from 1979 to 1988. The mean population was 205 000 and cross boundary flow of referrals was balanced; private patients were included. A total of 1000 catheterisation procedures were performed, 823 for coronary artery disease and 177 for valvar heart disease (VHD). Subsequently 497 patients underwent coronary artery bypass grafting (CABG) and 140 patients valvar surgery with or without CABG. With the exception of 1984, growth in the need for investigation of coronary artery disease and revascularisation has been continuous. Thus whereas the 10 year mean district requirement for coronary angiography was 401 procedures/million population/year the 1988 requirement was twice that (848). Likewise, whereas the 10 year mean requirement for bypass grafting was 242 operations/million population/year the figure for 1988 was 395 (estimated). Valvar investigation and surgery showed little change over the period; 18 (SE 1·9) patients were investigated annually, and 14·3 (1·3) underwent surgery. Figures/million population/year are 88 and 70 respectively.

North West Surrey has a standardised mortality ratio (SMR) of 0·78 for ischaemic heart disease and of 1·0 for VHD. Extrapolation towards the current national need for invasive investigation seems to approach 1200 procedures/million population/year. The extrapolated current need for coronary artery surgery approaches 500 operations/million population/year. As the mean age of the population of the district is lower than the national average the predictions for valvar heart disease may be skewed. The national target for 1990 for CABG is 300 operations/million/year.

Comparative study of left ventricular structure and function in elite athletes

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Adaptations to left ventricular (LV) structure and function in athletes seems to be dependent on the type, intensity, and duration of exercise training. We therefore studied two clearly defined groups of elite athletes by M mode and Doppler echocardiography, with a group of sedentary subjects as controls. All groups were age and sex matched. Group 1 comprised 10 elite endurance athletes with mean maximal oxygen consumption ($\dot{V}o_2$max) 74·7 (SD 4·8) ml/kg/minute. Group 2 comprised 10 elite weightlifters with mean maximal $\dot{V}o_2$max 45·3 (6·6). Group 3 comprised 10 sedentary individuals with $\dot{V}o_2$max 44·5 (7·0). Left ventricular end diastolic dimension was significantly higher in group one (5·72 (0·23)) than in group 2 or 3 (5·29 (0·29), 5·19 (0·31) respectively, $p < 0·001$). Left ventricular mass index was significantly higher in groups 1 and 2 (156·4 (19·8), 138·6 (24·1) respectively) than in group 3 (104·1 (10·5), $p < 0·001$). Percentage fractional shortening was used as an index of systolic function, and no significant difference was found between the groups. Doppler E/A ratio was taken as an index of diastolic function and was significantly raised in group 1 at rest (3·37 (0·81)) compared with groups 2 and 3 (2·12 (0·76), 1·99 (0·34) respectively, $p < 0·003$). On exercise the E/A ratio in group 1 was significantly higher than in group 3 (1·95 (0·48) and 1·23 (0·16), $p < 0·001$) and tended to be higher than in group 2 (1·68 (0·49), NS).

These data show that both modes of intense training produce left ventricular hypertrophy. Diastolic function is enhanced in the endurance trained athletes but not in the weightlifters.

Myocardial flow and function in microvascular angina

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Patients who have typical anginal chest pain but who have angiographically normal coronary vessels present a major clinical problem. Ten patients, three male and seven female, with typical exertional angina and abnormal exercise thallium scans underwent angiography and were found to have entirely normal vessels with no evidence of coronary artery spasm. Myocardial flow was assessed using xenon washout. Xenon was injected into the coronary artery under direct vision, and scans were obtained with a mobile gammacamera fitted with a biplane collimator. Distribution within the myocardium was assessed, and flow was calculated from washout curves using peak to 30 seconds and applying the Kety formula. At rest right coronary artery and left coronary artery distribution and flows were within normal limits; RC flow 55·5 (8·8), left anterior descending 66·6 (11·3), and circumflex 62·3 (9·9) ml/100 g/minute. With atrial pacing to a heart rate similar to that achieved during exercise, chest pain occurred in all patients. Distribution volume fell in at least one coronary distribution in all patients, and this was associated with reduced coronary flow by a mean of 28·6 (9·8)% ($p < 0·05$). By gating the scans to the electrocardiogram and reconstructing list mode data into a representative cardiac cycle, wall motion can be obtained from the same data that produced the washout curves. Areas of reduced distribution and flow were associated with reduced wall motion in all 10 patients.

These results suggest that in these patients a combination of reduced myocardial flow and associated wall motion abnormalities constitutes an ischaemic response, presumably at the microvascular level.

Interaction between cycle length and ventricular loading conditions on repolarisation

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Alteration in the normal time sequence of ventricular repolarisation encourages arrhythmia formation. There is evidence that the timing of ventricular repolarisation is not only dependent on cycle length (restitution process) but also on loading conditions (contraction-excitation feedback). This study aimed at examining a possible interaction between the two by comparing the timing of repolarisation of premature beats (cycle length 350 mseconds) with that of paced steady state beats (cycle length 700–850 mseconds) under altered conditions of ventricular loading. We recorded monophasic action potentials from the left ventricular endocardium as a measure of the time course of repolarisation with a catheter that incorporates a micromanometer sensor for recording ventricular pressure. The Valsalva manoeuvre was employed to alter ventricular loading whereby forced expiration impedes venous return and peak systolic pressure falls. Our observations were made during the early part of the Valsalva manoeuvre, before significant autonomic effects occur. Steady state atrial pacing was established. An early beat of cycle length 350 mseconds was interposed during a steady state pacing train before the start of the procedure and again during the low pressure phase. Peak systolic pressure for the steady state beats fell from 134 (SD 23) to 97 (30) mm Hg and for the early beats from 97 (23) to 66 (28) mm Hg. Under control conditions before the Valsalva manoeuvre monophasic action potential duration as measured at 90% repolarisation was shorter in the premature beats than in the control beats by 9 mseconds (298 (17) *v* 289 (13) mseconds). During the Valsalva manoeuvre at the lower pressures monophasic action potential duration was shorter in the premature beats than the preceding beats by 22 mseconds (303 (14) *v* 281 (20) mseconds).

Our results show that changes in ventricular loading alter the normal differences in repolarisation in response to an abrupt shortening in cycle length. These findings may be important in the genesis of arrhythmias initiated particularly by premature beats.

Postprandial hypotension and splanchnic vasodilatation are prevented by octreotide in patients with primary autonomic failure

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We studied the haemodynamic responses to a liquid meal in eight patients with primary autonomic failure before and after octreotide (SMS 201–995), which inhibits the release of gastrointestinal peptides. Subjects were studied while supine, in a temperature controlled laboratory (23 (1)°C), after a 12 hour fast. Saline placebo (0·5 ml) or octreotide (50 μg) was injected subcutaneously 30 minutes before a balanced liquid meal (66 g carbohydrate, 22 g fat, and 18 g protein), and measurements were made for 60 minutes. Blood pressure (BP) heart rate (HR) (Sentron), cardiac index (CI, assessed with continuous wave Doppler ultrasound (Exerdop)), forearm blood flow (FBF, assessed with strain gauge plethysmography), digital skin microvascular flow (LDF, assessed with laser Doppler flowmetry (Periflux, PF2b)) were measured non-invasively. Superior mesenteric artery blood flow (SMABF) was measured by a real time sector scanner and pulsed Doppler flowmeter (Ultramark 8 ATL). After placebo and the meal mean arterial pressure (MAP) fell (122 (8) to 99 (9) mm Hg, $p < 0\ 05$). SMABF rose (0·41 (0·05) to 0·743 (0·148) l/minute, $p < 0·05$) and superior mesenteric artery vascular resistance (SMAVR) fell (371 (94) to 167 (33) units, $p < 0\ 05$). There were no other haemodynamic changes. After octreotide there was a transient rise in MAP (118 (6) to 135 (8) mm Hg, $p < 0·05$). SMABF fell (0·497 (0·03) to 0 40 (0·03) l/minute, $p < 0·05$) and SMAVR rose (240 (19) to 370 (26) units, $p < 0·05$). There was no change in HR, CI, FBF, and LDF. After octreotide, ingestion of food did not change MAP (127 (7) to 125 (9) mm Hg), SMABF (0 373 (0 04) to 0 323 (0·04) l/minute), SMAVR (352 (19) to 386 (31)), or other haemodynamic variables.

We conclude that in patients with autonomic failure ingestion of food increases SMABF and reduces SMAVR, which probably contributes to the fall in BP, especially as there is no compensatory rise in HR, CI, and FVR, as observed in normal subjects. Octreotide prevents superior mesenteric artery vasodilatation and postprandial hypotension, probably through inhibiting the release of vasodilatory gastrointestinal peptides.

Changes in ultrafilterable and non-filterable serum magnesium concentrations after acute myocardial infarction

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To describe changes occurring in the free and protein bound plasma magnesium concentrations after acute myocardial infarction, 30 patients admitted with a diagnosis of suspected acute myocardial infarction (AMI) had serum total magnesium (TMg) and ultrafilterable magnesium (UfMg) concentrations estimated on five separate occasions over two days. Fourteen patients were subsequently shown to have had an AMI whereas the remaining 16 with an alternative diagnosis formed a control group. At the time of admission mean (SE) TMg concentration was 0·853 (0·025) mmol/l in the control group and 0·774 (0·018) in the infarct group, representing a deficit of 9·26% ($p < 0·02$). Mean UfMg concentration at admission was 0·638 (0 019) mmol/l in the control group and 0·585 (0·014) mmol/l in the infarct group, a deficit of 8·31% ($p < 0\ 05$). Mean non-filterable magnesium (NfMg) concentration was 11 68% lower in the infarct group, though this difference was not significant ($p < 0·10$). In patients with AMI mean TMg concentration rose by 0·072 mmol/l (9·3%; $p < 0\ 02$) and NfMg concentration by 0·02 mmol/l (10·6%; $p < 0·05$) over the first 48 hours while no significant change in UfMg concentration was noted. In contrast, TMg concentration fell by 0·044 nmol/l (5·2%; $p < 0\ 02$) in the control group with no change in UfMg and NfMg concentrations being observed. Mean venous H$^+$ concentration fell by 6%, from 48·8 (1 31) nmol/l to 4·10 (0·86) nmol/l in patients with AMI. This change showed a significant negative correlation with the observed increase of mean NfMg concentration ($R = 0\ 903$; $p < 0·05$).

In contrast to the previously reported changes occurring in TMg concentration after AMI, we found that the physiologically active ultrafilterable magnesium component remains stable during the early postinfarct period. Our data additionally suggest that displacement of Mg^{2+} from its protein binding sites, by H$^+$, may be important in producing buffering of UfMg.

Platelet activating factor antagonist protects the heart from arrhythmias and limits the extent of myocardial infarction during early ischaemia

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There is increasing evidence that platelet activation aggravates the effects of coronary artery occlusion (CAO). To investigate this we examined the effects of inhibition of platelet activating factor (PAF) during 30 minutes' CAO in the rabbit on haemodynamics, infarct size, and arrhythmias. Infarct size was measured in four left ventricular (LV) sections of equal thickness and was expressed as percentage zone at risk (obtained in 10 separate hearts after 90 minutes CAO). In the control group ($n = 10$) CAO produced an immediate decrease in arterial pressure (100 (2) mm Hg to 91 (3) mm Hg, $p < 0·01$) while heart rate (HR) remained unchanged (NS) and half developed ventricular fibrillation (VF). The extent of infarction in each section was 52 (2)%, 54 (2)%, 44 (2)%, and 35 (2)% from base to apex and 46% of total LV. After pretreatment with the PAF antagonist BN 50739, 10 mg/kg intravenously ($n = 10$), CAO produced little change in arterial pressure (93 (3) mm Hg to 86 (5) mm Hg) and HR (both NS), and a fifth developed VF. The extent of infarction was significantly reduced in each section (36 (1)%, 43 (2)%, 32 (1)%, and 26 (1)% from base to apex and 34% of total LV ($p < 0·001$ *v* untreated group).

These results indicate that use of a PAF antagonist can attenuate the extent of myocardial necrosis and the incidence of ventricular arrhythmias during early stages of acute myocardial infarction.

Differential expression of ventricular proto-oncogenes in three models of cardiac hypertrophy

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Various stimuli, including pressure and volume overload, result in cardiac hypertrophy. To investigate the role of proto-oncogene products in signal transduction in myocardial growth we compared hypertrophy in three rat models with changes in ventricular H-ras, c-myc and c-fos messenger (m) RNAs measured by hybridisation to specific complementary (c) DNAs. Left ventricular (LV) pressure overload induced by aortic constriction increased heart weight and LV proto-oncogene mRNAs at three days compared with controls (H-ras 1·5 (0·2) *v* 0·6 (0·2) optical density (OD) units/total mRNA, p < 0·01; c-myc 1·3 (0·2) *v* 1·0 (0·1), p < 0·05; c-fos 2·9 (0·5) *v* 1·0 (0·1), p < 0·05; mean (SE), n = 8). In genetically hypertensive rats, despite established hypertrophy, no changes in LV mRNAs were found at five or 12 weeks, but right ventricular (RV) mRNAs were reduced compared with controls (H-ras five weeks, 0·14 (0·07) *v* 0·96 (0·04), p < 0·01 and 12 weeks 0·03 (0·01) *v* 0·22 (0·04), p < 0·01; c-myc five weeks 0·29 (0·12) *v* 0·97 (0·04), p < 0·01, and 12 weeks 0·06 (0·007) *v* 0·22 (0·03), p < 0·01; n = 8), suggesting reduced RV load. Marked LV and RV hypertrophy resulting from thyroid hormone treatment (triiodothyronine 50 µg daily for 14 days) was associated with increased LV c-fos (0·63 (0·1) *v* 0·33 (0·08), p < 0·05) and RV myc and fos (c-myc 0·95 (0·09) *v* 0·43 (0·13), p < 0·01; c-fos 0·8 (0·04) *v* 0·32 (0·03), p < 0 01, (n = 8), consistent with continuing changes in LV and RV volume load.

Cardiac refashioning is associated with different effects on pretranslational expression of specific proto-oncogenes in the left ventricle and right ventricle, while established hypertrophy can be found without maintained proto-oncogene stimulation. These findings provide insight into the mechanisms of cardiac growth and potential for controlling the hypertrophic process in disease states such as hypertension.

Effects of captopril on arrhythmias and cellular electrophysiology during low flow ischaemia and reperfusion

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Treatment with captopril reduces the ventricular arrhythmias recorded from patients with severe heart failure and is associated with improved mortality. To investigate the cellular electrophysiological (CEP) effects of captopril we studied isolated guinea pig hearts paced at 3·3 Hz and perfused at 32°C with oxygenated Krebs solution containing captopril: group 1 (n = 6) 10^{-4} mol/l, group 2 (n = 7) 10^{-6} mol/l, group 3 (n = 6) 10^{-8} mol/l, and untreated controls (n = 7). After 20 minutes perfusion at 7 ml/minute there were no differences in perfusion pressure. During ischaemia (flow reduced to 10% for 30 minutes) ventricular tachycardia or ventricular fibrillation occurred in: 4/7 controls, 1/6 group 1, 1/7 group 2, and 0/6 group 3. Reperfusion (flow returned to 7 ml/minute for 15 minutes) ventricular tachycardia or ventricular fibrillation occurred in 6/7 controls but in none of the treated hearts. There were no resting differences in CEP effects between right ventricle (RV) and left ventricle (LV). Captopril had no detected effect on baseline CEP recordings, using floating microelectrodes, but attenuated the ischaemia induced shortening of: (*a*) action potential duration (APD)—for example, RV APD_{95} (mseconds) at 20 minutes: group 2, 123 (6) (p < 0·05); group 3, 107 (3); control, 104 (4); and at 30 minutes: group 2, 111 (3) (p < 0·01); group 3, 101 (3); control, 91 (4); LV APD_{95} (mseconds) at 20 minutes: group 2, 112 (4) (p < 0·02); group 3, 99 (2); control 97, (3); and at 30 minutes: group 2, 103 (4) (p < 0·02); group 3, 94 (4); control, 92 (1); and (*b*) refractory period (msecond)—for example, at 15 minutes: group 2, 123 (2) (p < 0·001); group 3, 119 (3); control, 114 (4); and at 30 minutes: group 2, 112 (4); group 3, 112 (3) (p < 0 05); and control, 104 (1). All groups recovered to normal on reperfusion.

These results suggest there is a dose dependent cellular electrophysiological basis to the antiarrhythmic action of captopril.

Do monounsaturated fatty acids have a role in restenosis after coronary angioplasty?

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Recent work has suggested that a diet enriched with fish oils may reduce restenosis after coronary angioplasty. The object of this study was to determine whether there was any association between the long term intake of fatty acids, as reflected by the fatty acid composition of subcutaneous fat, and restenosis after percutaneous transluminal coronary angiopathy. Eighty two patients who had undergone successful single vessel angioplasty were studied. All underwent angiographic follow up. The fatty acid composition of the subcutaneous fat was determined by gas liquid chromatography. Restenosis occurred in 37 (48%). The concentrations of the monounsaturated fatty acids were lower in those who had restenosis. The percentage of palmitoleic acid was 5·8 (2·28)% in those who had restenosis, and 7·1 (2·44)% in those who did not (p < 0·001). The percentage of oleic acid was 41·0 (3·3)% in those who had restenosis and 42·5 (4·18)% in those who did not (p = 0·08). The percentage of the saturated fatty acid palmitic acid was increased in those who had restenosis compared with those who did not (24·7 (2·92)% and 23·7 (2·23)% respectively, p = 0·06). There were no other differences in the subcutaneous fatty acid composition of the two groups.

These results lend support to the recent suggestion that monounsaturated fatty acids may have a protective role in relation to the development of coronary arterial disease.

Antiarrhythmic benefits of left ventricular preload reduction

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Ventricular stretch may play an important part in arrhythmogenesis in heart failure. Though stretch is known to influence action potential duration in isolated muscle strips, it remains uncertain whether haemodynamic changes in the whole heart can influence action potential duration. We studied the effects of left ventricular pressure changes in an isolated working heart preparation. Guinea pig hearts ($n = 23$) were perfused via the left atrium, ejecting against an aortic afterload. Left ventricular diastolic and systolic pressures were varied independently. Intracellular potentials were recorded from the epicardium of the left ventricle with floating microelectrodes. An increase in left ventricular end diastolic pressure from 2·2 to 8·2 mm Hg, at constant systolic pressure, shortened action potential duration by 10·2 (SE 2·1) mseconds ($p < 0{\cdot}001$). After a change in pressure action potential duration reached a new steady state after 30 seconds. Changes were fully reversible. Increase in left ventricular peak systolic pressure from 60 mm Hg to 100 mm Hg, at constant diastolic pressure, caused a lesser degree of shortening of action potential (2·7 (0·6) mseconds, $p < 0{\cdot}002$). The gradients of the regression lines relating the shortening of action potential duration to the increase in end diastolic pressure and peak systolic pressure were −1 70 mseconds/mm Hg and −0·07 mseconds/mm Hg respectively.

Our findings show that changes in whole heart haemodynamic variables do influence action potential duration. They show a mechanism whereby changes in ventricular stretch may contribute to arrhythmogenesis in heart failure and suggest that preload reduction is more likely to prevent arrhythmias that afterload reduction.

Characterisation of the calcium release channel from human cardiac sarcoplasmic reticulum

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Release of calcium from the sarcoplasmic reticulum (SR) is central to excitation-contraction coupling in the mammalian heart and is controlled by the gating of a specific ion channel. The purpose of this study was to characterise the calcium released channel from human tissue by incorporating junctional SR vesicles into artificial planar phospholipid bilayers and recording their conductivity under voltage-clamp conditions. An additional objective was to investigate the possibility that the altered function of these channels contributes to the impairment of SR calcium release, previously reported in humans with end stage cardiac failure. Tissue was obtained from the explanted hearts of six patients (three with coronary disease and previous infarction and three with normal coronary arteries) undergoing transplantation for refractory cardiac failure, and preparations enriched with junctional SR membrane vesicles were isolated. A calcium channel was identified with a conductance of 101pS in 67 mM Ca^{2+}. Gating was modulated by alterations to the medium at the cytosolic face of the channel. Elevation of the Ca^{2+} concentration across the range 0·1–100 µM increased channel opening, as did the addition of millimolar ATP or caffeine. Millimolar magnesium or micromolar ruthenium red reduced channel opening. The plant alkaloid ryanodine bound irreversibly to the channel to produce a fixed open state with a reduced conductance (about 40%) relative to the unblocked open state. The ryanodine sensitive channel identified in this study has properties consistent with a role in excitation-contraction coupling through a process of calcium induced calcium release and is similar to equivalent channels from normal animal tissue.

We conclude that alterations to the properties of single calcium release channels do not seem to contribute to the abnormalities of SR function observed in heart failure.

Effect of low dose fish oil supplements on contraction and relaxation in the resistance artery

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There are conflicting reports on the effects of fish oil in hypertension and ischaemic heart disease. To date, animal studies have tended to use high doses of fish oil of little relevance to the amounts recommended in humans. Accordingly, we examined the effect of low dose (0·4% of total dietary calories) fish oil supplementation of a 40%, mainly saturated, fat diet (typical of Scottish eating habits) on α_1 adrenoceptor stimulated contractile function in resistance arteries. Two groups ($n = 10$) of male Sprague-Dawley rats were fed for eight weeks, one group receiving fish oil daily. This dose of fish oil significantly increases tissue phospholipid eicosapentaenoic acid concentration (138·8 (21·0) *v* 24·2 (6·5) µg/g, $p < 0{\cdot}01$). Femoral resistance arteries were dissected and mounted as rings in a myograph. Rats in the fish oil group showed highly significant increases in sensitivity to noradrenaline (estimated dose$_{50}$ 2·2 *v* 4·2 × 10^{-7}M, $p < 0{\cdot}001$) in the presence of 10^{-5} M timolol and 10^{-7} M yohimbine. Acetylcholine induced relaxation of preconstricted arteries was also significantly enhanced in the fish oil group (maximum relaxation 36% *v* 27%, $p < 0{\cdot}05$).

These data indicate that fish oil can effect both contractile and relaxing functions of resistance arteries in doses comparable to those given to humans.

Perception of angina in diabetes: relation to somatic pain threshold

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Patients with silent myocardial ischaemia may have a generalised non-segmental hyposensitivity to pain. It is not known, however, whether more subtle alteration in the perception of angina, as measured by anginal perceptual threshold, also reflects generalised hyposensitivity to painful stimuli. We exercised 45 patients (19 diabetic and 26 non-diabetic) to measure anginal perceptual threshold (the time from onset of 0·1 mV ST depression to onset of angina). Somatic pain threshold was measured by calf sphygmomanometry. The cuff was inflated rapidly until pain occurred, with six repeat inflations to test reproducibility. Because there was no significant difference between measurements (coefficient of variation 0·16) the mean value in each patient provided a measure of somatic pain threshold. The median value for anginal perceptual threshold was higher in the diabetic patients with a broader interquartile range (125 (100 to 163) *v* 12 (0 to 40) seconds, $p < 0{\cdot}01$). In the diabetic group there was a significant linear relation between anginal perceptual threshold and somatic pain threshold ($r = 0.5$, $p = 0{\cdot}03$), those patients with a higher somatic pain threshold having greater prolongation of the anginal perceptual threshold. In the non-diabetic patients, however, the range of values was lower, and no relation could be shown between these variables.

Thus, like patients with silent ischaemia, diabetic patients in whom the perception of angina is impaired have a generalised hyposensitivity to pain which, based on earlier observations, is caused at least in part by diabetic neuropathy.

Electrocardiogram correlates of early coronary artery patency and myocardial perfusion after thrombolysis

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An early fall in the ST segment is recognised in patients receiving thrombolytic treatment. The sensitivity and specificity of this fall in detecting reperfusion remain controversial and require further validation in a large patient group. One hundred and four patients (82 men, 22 women, age range 31–69) with acute myocardial infarction of ≤6 hours' duration received thrombolytic treatment (anistreplase 30 mg ($n = 53$), 1·5 MU streptokinase ($n = 51$)). Coronary angiography at 90 minutes showed a patent artery (TIMI 2,3) in 64 of the 104 (61·5%) and occlusion (TIMI 0,1), in 40 (38·5%). Twelve lead electrocardiograms (ECGs) were performed before and two and four hours after thrombolysis. Data from each ECG were digitised and the parameters stored on computer. Fractional change (FC) (% fall in ST segments) was calculated for the single lead with maximal ST elevation and for $\sum$ST elevation across all leads. An FC value ≥0·5 calculated at two hours from a single lead was more sensitive in detecting reperfusion than FC_2 calculated from $\sum$ST elevation (81% *v* 75%) and more specific (60% *v* 55%). All arteries performed well (FC_2 sensitivity and specificity respectively: left anterior descending 81·5% and 55·5%; right coronary, 81% and 67%; circumflex, 83% and 50%). Ten patients with an occluded artery at angiography had collateral supply to the distal infarct related artery and four of them had an FC ≥0.5, suggesting adequate perfusion of myocardium despite no anterograde reperfusion.

An FC value ≥0·5 two hours after starting treatment calculated from a single lead suggests (re)perfused myocardium and is helpful in directing further treatment.

Cardiac reserve and prognosis in cardiogenic shock

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The hypothesis that the prognosis in patients with cardiogenic shock is primarily dependent on cardiac pumping reserve was tested in a prospective study of consecutive patients with a clinical diagnosis of cardiogenic shock treated medically. Twenty eight patients were included, and their haemodynamic state was assessed with thermodilution Swan-Ganz catheters and arterial cannulas. The cardiac pumping reserve was evaluated by the response of the failing heart to graded incremental dobutamine infusion (2·5–40 μg/kg/minute) after optimising left ventricular preload. The patients were followed up for at least one year: 11 survived longer than one year, and the rest died within that period. The patients were indistinguishable by clinical and basal haemodynamic criteria. When the responses to dobutamine stimulation were considered, however, clear separation of the cardiac reserve of survivors and non-survivors was obtained. All patients with limited reserve—that is, with peak stimulated cardiac power output of <1·0 W or peak left ventricular stroke work index of <0.25 $J.m^{-2}$—died, and all patients with values above both these levels were able to survive longer than the one year follow up.

Thus this study showed that haemodynamic evaluation of cardiac reserve can provide objective criteria for predicting the prognosis of individual patients with cardiogenic shock. The availability of such a prognostic indicator will be invaluable in formulating management plans for these patients.

Angiographic findings and prognosis in unstable angina associated with T wave inversion in anterior chest leads

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It has been proposed that the presence or development of deep symmetrical T wave inversion in the precordial leads in patients with unstable angina is indicative of critical reduction of flow in the left anterior descending (LAD) coronary artery. This has been associated with a poor short term prognosis, and therefore early investigation and revascularisation have been advocated. We report the angiographic appearances in 53 patients with this condition attending two centres. A very severe stenosis was found in the LAD artery in all except one patient; 62% had single vessel disease, 25% double vessel disease, and 11% triple vessel disease. One patient had an occlusion of the right coronary artery only. Urgent revascularisation of such patients has not been routinely practised at one centre. We have reviewed 26 patients admitted to the coronary care unit there between 1984 and 1989 with these clinical characteristics and electrocardiographic pattern (16 of whom had undergone coronary angiography) who were treated medically during their initial admission. Of these, 13 were still alive and had not progressed to infarction (mean follow up 41 months). Seven patients had had anterior myocardial infarction at a mean of 18 months (one of whom died). Six required elective revascularisation at a mean of six months (none within two months).

We have confirmed that this electrocardiographic pattern is highly predictive of significant disease in the LAD artery. It is not clear whether urgent revascularisation should be routinely employed in the early management of these patients.

Human α calcitonin gene related peptide improves exercise workload to ischaemia and dilates stenoses of the epicardial coronary artery

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Six patients (aged 54–67) with effort angina and normal left ventricular function received intravenous infusions of placebo and human α calcitonin gene related peptide (CGRP) (50 pmol/minute for 10 minutes) before and during treadmill exercise testing. Rate-pressure product (RPP) at 0·1 mV ST segment depression was 201·4 (46·0) and 241·0 (90·7) beats/min/mm $\text{Hg}/10^{-2}$ ($p < 0{\cdot}05$) and at peak exercise was 238·2 (83·7) and 264·0 (80·5) beats/min/mm $\text{Hg}/10^{-2}$ ($p < 0{\cdot}05$) with placebo and CGRP respectively. Exercise duration to 0·1 mV ST segment depression and peak exercise were similar on both infusions. Cardiac catheterisation was performed with right atrial pacing at a rate up to 20 beats/min above the resting rate; aortic, pulmonary artery, right atrial and pulmonary wedge pressures, left ventricular end diastolic pressure (LVEDP) and its rate of change (dP/dt) were recorded during consecutive intravenous infusions of placebo and CGRP for 10 minutes at the same rate as before. Systemic vascular resistance index was lower with CGRP compared with placebo (34·6 (15·6) *v* 44·6 (14·4) units.m^2, $p < 0{\cdot}05$). Cardiac index was greater ($p < 0{\cdot}05$) with CGRP (3·84 (0·5) l/minute/m^2) compared with placebo (3·38 (0·5) l/minute/m^2). There was no significant change in aortic pressure, LVEDP, dP/dt, or pulmonary vascular resistance index. Incremental atrial pacing to angina or 0·2 mV ST segment depression disclosed no difference in RPP at 0·1 mV ST segment depression with placebo and CGRP. Quantitative analysis of selected coronary artery stenoses showed an increase in stenosis diameter from 1·14 (0·16) to 1·57 (0·33) mm ($p < 0{\cdot}05$) and in reference diameter from 2·16 (0·30) to 2·54 (0·37) mm ($p < 0{\cdot}05$) with placebo and CGRP respectively.

Thus intravenous CGRP increases cardiac workload to 0·1 mV ST segment depression and peak exercise, which implies an increase in the coronary flow reserve on exercise, not present on pacing. It dilates both stenosed and normal segments of the coronary arteries at rest.

Exercise testing after thrombolytic treatment in acute myocardial infarction: reciprocal ST changes and diagnostic specificity

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Thrombolytic treatment modifies the evolution of myocardial infarction, but its effect on the exercise electrocardiogram (ECG) for risk stratification is unknown. We analysed predischarge exercise ECGs in 40 patients with acute infarction (23 anterior and 17 inferior) treated with streptokinase. Coronary arteriography within two weeks confirmed disease of the infarct related artery in every patient, with additional remote disease (⩾70% stenosis) in 45% of patients. The exercise ECG showed ST depression (⩾0·1 mV) in 30 patients, only three of whom experienced angina. Exertional ST elevation in the infarct territory was common, occurring in 26 patients, 18 of whom had additional ST depression in the contralateral territory. Of these, only seven had remote coronary disease and in the remainder ST depression occurred as a purely electrical phenomenon. Thus the sensitivity of exertional ST depression for the diagnosis of coronary disease remote from the infarct related vessel was 76%. The specificity was, however, only 25% because of the high incidence of false positive reciprocal ST depression.

In conclusion, exertional ST elevation in the zone of infarction occurs commonly after thrombolytic treatment. It is often associated with reciprocal ST depression, although remote coronary disease is found in fewer than 40% of these patients. Thus the specificity of exercise electrocardiography for coronary disease remote from the zone of infarction is reduced by thrombolytic treatment while sensitivity is largely unaffected. These data indicate a need for reappraising exercise ECG criteria for risk stratification after acute myocardial infarction treated with thrombolytic agents.

Evaluation of cardiac transplantation for cardiomyopathy in children

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Thirty seven children underwent cardiac transplantation for cardiomyopathy (dilated 26, hypertrophic eight, restrictive three) and were followed up for a minimum of one year. The age at transplantation ranged from 6 months to 14 years (mean 7·4 years). Nine patients were less than 2 years of age. The hospital survival was 86% (32/37). Causes of death were right side heart failure secondary to increased pulmonary vascular resistance in four and hyperacute rejection in one. Immunosuppression consisted of cyclosporin and azathioprine treatment without routine steroids. Routine biopsy was not performed in children below 12 years of age. There were three late deaths at 1, 3½, and 4 years. The 29 survivors, with a mean follow up of 36·6 (12–64) months, were free of symptoms (New York Heart Association class I). Renal dysfunction requiring discontinuation of cyclosporin treatment occurred in only one patient. Two patients were given long term antihypertensive treatment. Two patients developed B cell lymphoma, which was localised to the abdomen in one and to the tonsils in the other; both lymphomas regressed completely with a reduction in level of immunosuppression and intravenous acyclovir concentration. Annual cardiac catheterisation showed normal left ventricular function and absence of angiographic coronary artery disease. Change in aortic root dimension towards the appropriate size for age and weight of the child was shown by echocardiography. The majority of patients showed a satisfactory growth pattern. Cognitive function was within the normal range, but the rate of late behaviour disturbances was higher than the normal population (25% *v* 10%). Twelve of the 13 children of school age returned to school.

We conclude that medium term results of cardiac transplantation for cardiomyopathy in children are encouraging.

Class II major histocompatibility complex molecules on cardiac endothelium: an early biopsy marker of rejection in the transplanted human heart

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The role of major histocompatibility complex (MHC) class II molecule expression in the rejection of the transplanted human heart is controversial. To assess whether MHC class II expression precedes histological evidence of rejection we studied 63 sequential endomyocardial biopsy specimens from 13 patients 24–390 days after orthotopic cardiac transplantation. Histological rejection was graded according to Stanford criteria. MHC class II expression on endothelial cells was assessed by double immunofluorescence with monoclonal antibodies to class II molecules and antiserum to human factor VIII as endothelial cell marker. Class II molecule expression was independently scored as absent (0), low (1+), or high (2+). Rejection grade was 0 in 38 endomyocardial biopsy specimens (60%), 1 in 18 (28%), and 2 in seven (11%). Class II expression score was 0 in 19 biopsy specimens (30%), 1+ in 27 (43%), and 2+ in 17 (27%). There was no relation between the 63 MHC scores and the severity of histological rejection in the corresponding biopsy specimen. The MHC scores of the 38 endomyocardial biopsy specimens with no histological rejection were compared with the histological grade of biopsy specimens taken in the following two to four weeks; 8/9 with a high MHC score (2+) were subsequently rejected *v* 5/29 with absent or low MHC expression (score 0, +1) (p < 0·001). The sensitivity, specificity, predictive value, and accuracy of MHC score 2+ as a predictor of rejection was 61%, 96%, 89%, and 84% respectively.

High grade MHC class II molecule expression on cardiac endothelial cells is an early biopsy marker of subsequent rejection and may be a useful adjunct to routine histological assessment. Cardiac endothelial cells expressing MHC class II molecules may have an active role in first set allosensitisation and initiation of rejection of the cardiac allograft.

Coronary angioplasty in cardiac transplant recipients

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Accelerated coronary artery disease continues to be one of the most important problems after cardiac transplantation. Because of the diffuse nature of the disease the only treatment applied to date has been retransplantation. We performed balloon angioplasty on nine patients with coronary artery disease judged suitable for revascularisation at a mean of 36 months (range 15–87 months) after orthotopic transplantation; the mean age of the patients was 42 (range 21–58). This constitutes 18% of transplant recipients with significant coronary disease at our institution. Two patients had symptoms of angina, both developing ST segment change on exercise testing. Three patients had significant disease (> 50% luminal narrowing) in one vessel and the remaining six had three vessel disease. A total of 16 lesions were dilated, angioplasty being undertaken in the left anterior descending artery in seven patients, the right coronary artery in two, and the circumflex artery in four. Single lesion dilatation was performed in three cases, two lesion dilatation in five, and three lesion dilatation in one. Primary angiographic success was achieved in 15 lesions. Revascularisation was unsuccessful in one lesion, and one patient developed ventricular fibrillation during balloon inflation. After 13 months of follow up (range 5–51 months) one patient had recurrent angina. Seven patients were restudied, of whom two developed restenosis. One underwent a second successful angioplasty and the other had bypass surgery.

These data indicate that coronary angioplasty in transplant recipients can be successfully undertaken with an apparent low restenosis rate. The influence of this procedure on the ultimate prognosis remains to be determined.

Resolution of pulmonary hypertension after single lung transplantation

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The benefits of single lung transplantation on pulmonary haemodynamics and right ventricular function have not previously been described. Five patients underwent cardiac catheterisation at a mean of 18 months after transplantation for fibrosing alveolitis. Four had preoperative data for comparison. Mean pulmonary artery pressure fell by 46% (33·25 (3·75) to 17·75 (1·25) mm Hg; p = 0·039) and peak right ventricular systolic pressure by 38% (52·75 (5·11) to 32·5 (1·66) mm Hg; p = 0·013). There was no significant change in pulmonary artery wedge pressure or cardiac output. Total pulmonary resistance fell by 52% (6·33 (0·85) to 3·04 (0·17) Units; p = 0·022) and pulmonary arteriolar resistance by 62% (5·01 (0·8) to 1·92 (0·25) Units; p = 0·021). In all patients there was an improvement in right ventricular function assessed by contrast ventriculography, and all were normal after transplantation. A fifth patient, who was not catheterised preoperatively, had normal pulmonary pressures, arteriolar resistances, and right ventricular function.

This study shows that even in patients with moderate pulmonary hypertension and impaired right ventricular function due to lung disease single lung transplantation may be performed with success. In such patients, right heart pressures, pulmonary resistances, and right ventricular function return to normal.

Total and differential blood flow measurement in pulmonary arteries of patients with single lung transplantation: a magnetic resonance study

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Magnetic resonance imaging was used to measure total and differential pulmonary arterial blood flow in nine patients with single lung transplantation and in nine volunteers matched for age and sex. Spin echo images were acquired in transverse and oblique planes parallel and perpendicular to the mean pulmonary artery and right and left pulmonary arteries. Magnetic resonance velocity mapping was used to measure velocity profile and to estimate pressure gradient across the anastomoses. Quantitative blood flow was also measured in the mean, right, and left pulmonary arteries. Arterial blood flow to the transplanted lungs was 2·07 (0·45) l/min/m^2 in the group with right side transplantation and 2·43 (0·60) l/min/m^2 in the group with left side transplantation compared with 1·22 (0·22) l/min/m^2 and 1·27 (0·41) l/min/m^2 in the control groups respectively. The ratio of blood flow in the transplanted and the native lungs in all patients studied was 2·8 (0 83). The estimated pressure gradient across vascular anastomoses was 4–25 mm Hg.

The flow patterns in the pulmonary arteries of transplanted and native lungs are of particular interest. The flow pattern in transplanted lungs has a wide forward flow during systole and most of diastole, whereas that in native lungs has a narrow forward flow with early systolic peak and a reverse flow during late systole and most of diastole. This differential flow and its pattern is related to the relative resistance in the two lungs. Sequential studies of pulmonary blood flow using this non-invasive technique could be useful in managing patients with single lung transplantation.

Host generated neointimal linings within an implantable textured surface left ventricular assist device (433 total patient days)

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Implantable left ventricular assist devices with textured blood contacting surfaces were recently implanted in six patients (aged 22 to 52) for 35, 37, 41, 84, 114, and 132 days with no thromboembolic complications. All patients successfully received transplants. The Thermo Cardiosystems device features an integrally textured fibrillar polyurethane (ITP) diaphragm on a pusher plate and sintered titanium microspheres (STM) on the static housing. These surfaces encourage the adherence and formation of an organising coagulum, which serves as the foundation for subsequent neointimal development. After excision, samples for light microscopy, electron microscopy, and immunocytochemical evaluation were collected from identical areas of the ITP and STM surfaces. Devices were free of thrombus and calcification. The linings were thin and transparent, with areas of collagenous deposition. The STM surface became progressively covered with islands of collagen adjacent to areas of compact fibrin. The ITP surface contained more cells but fewer islands of collagen. Transmission electron microscopy showed some cells to have the appearance of activated macrophages while others were producing tropocollagen. On the ITP surface multinucleated cells with dense inclusion bodies and multiple pseudopodia were observed. Immunocytochemical techniques showed that the cells from both surfaces were of mesenchymal and not endothelial or smooth muscle origin.

These linings seem satisfactory in intermediate clinical use and warrant further evaluation in systems being designed for permanent implantation.

Feasibility and acceptability of day case permanent pacing

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Fifty patients requiring permanent pacing or generator change were randomly assigned to either conventional inpatient management or same day discharge day case management. Twenty-four (mean age 73 2 years) were managed conventionally and 26 (mean age 73·7 years) as day cases. Two in the day case group could not be discharged on the same day, one because of haematoma and one because the family refused. Mean hospital stay in the remainder was 5·7 hours (day case) and 70·0 hours (conventional). There was only one other complication in the day case group—an electrode dislodgement after discharge. In the conventional group there were two electrode dislodgements (one atrial displacement and one ventricular threshold rise assumed to be secondary to a microdislodgement), one infection requiring the procedure to be redone, and one pneumothorax. One patient in the conventional group died of ruptured aortic aneurysm five days after discharge. A questionnaire designed to assess how acceptable patients found the procedure gave an equal result (8·8/10) for each group. There were no significant differences between the two groups in the number of consultations with general practitioners in the month after pacing or in acceptability (Mann-Whitney U test). To assess the significance of the complication rates sample size calculations indicate the study would have required 2500 subjects. The saving per patient with day case management was between £400 and £650.

Day case pacing is feasible in the United Kingdom, is acceptable to patients, and has considerable economic advantages.

Randomised double blind crossover study of four rate responsive pacing modes

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Rate responsive pacing has known haemodynamic advantages over fixed rate but no direct comparison of modern RR modes has been undertaken. Twenty two patients aged 18–81 years (mean 52) had activity sensing DDDR pacemakers (PM) implanted. All showed second or third degree atrioventricular block, seven with retrograde ventriculoatrial conduction and 17 with sinus node incompetence at implantation. Patients were randomised to VVIR, DDIR, DDD, or DDDR for four week periods in a double blind crossover design. They were then assessed subjectively, with symptom and functional state questionnaires and visual analogue scales, and objectively, by graded exercise treadmill testing and while performing standardised daily activities continuously monitored electrocardiographically. Five patients demanded early crossover, all from VVIR mode. Most patients (13) preferred DDDR, four preferred DDIR (three after His ablation), four preferred any dual mode, and one patient with poor left ventricular function preferred VVIR. Perceived general wellbeing was worse in VVIR than DDD ($p < 0{\cdot}05$) and DDDR ($p < 0{\cdot}01$) but not than DDIR (NS). Subjective exercise capacity was worse in VVIR than in dual chamber modes ($p < 0{\cdot}05$). Objective assessment showed, however, that mean exercise treadmill times were similar in all modes. Percent change in heart rate during standardised daily activities was also similar in all modes, except during mental stress when VVIR significantly underresponded ($p < 0{\cdot}001$).

Thus, most patients prefer DDDR, but objective exercise and standardised daily activity parameters are similar in all four RR modes.

Complications associated with retained defunct pacemaker leads

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The incidence and type of complications associated with retained, defunct pacemaker leads is reported in 118 patients seen at this unit between 1978 and 1989. Sixty four women and 54 men (mean age 66 years, range 9–94) were classified according to the reason for intervention resulting in lead retention as (*a*) lead failure (group A, 65 patients) or (*b*) infection of the pacing system (group B, 53 patients). Follow up ranged from 1 month to 192 months (mean 67) in group A and from 5 months to 162 months (mean 62) in group B. Total mortality was 28% in each group; pacemaker related mortality was 0 in group A and 5·7% (3 patients) in group B (all three patients died of septicaemia). Major complication occurred in one patient (1·5%) in group A and in 22 patients (42%) in group B: one patient in group A and 10 patients in group B had recurrent local infection requiring surgery under general anaesthesia or cardiopulmonary bypass; nine patients in group B had septicaemia and three patients in group B had the superior vena cava syndrome. Minor complication occurred in two patients (3%) in group A and five patients (9%) in group B: one patient in group A and three patients in group B had recurrent local infection, one patient in each group had lead extrusion, and one patient in group B required further intervention.

Our data suggest (*a*) that non infected pacemaker leads can be safely left in situ if removal is difficult and (*b*) that pacemaker lead removal is essential when the change in pacemaker system is dictated by infection.

Improved physiological sensitivity of the QT sensing, rate adaptive pacemaker with a non-linear algorithm

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The physiological sensitivity and specificity of rate adaptive pacing systems depend on the attributes of the biosensor and the algorithm that translates the input from the sensor into changes in pacing rate. In this study we describe the electrophysiological basis of a new non-linear algorithm for the QT sensing pacemaker and compare the pacing rate responses during treadmill exercise with simultaneous measurement of oxygen consumption ($\dot{V}O_2$) in 11 patients (mean 59 years, six females) randomly programmed to one month periods in the linear and non-linear algorithms by a double blind, crossover design. The time to a 10 beats/min increase in rate was significantly less with the non-linear algorithm (126 s *v* 255 s; $p = 0{\cdot}025$) but there were no significant differences in exercise duration, peak pacing rate, or peak $\dot{V}O_2$. The slopes of the individual regression lines for the pacing rate and $\dot{V}O_2$ relation, which indicated the amount of pacing rate change per unit change in oxygen consumption, showed a significant improvement in four cases. Rate oscillation occurred in seven patients in the linear algorithm and in two patients in the non-linear setting. Initial deceleration of the pacing rate at the onset of exercise occurred in seven patients in the linear algorithm and in four patients in the non-linear setting.

In conclusion, the non-linear algorithm results in a faster response time during exercise, fewer instances of rate instability, and a qualitative improvement in the pattern of pacing rate change as gauged by metabolic indices in 36% of patients. The problem of an initial fall in rate, however, remains and is a function of the sensor rather than the algorithm.

Rate response to intravenous isoprenaline is an accurate predictor of chronotropic incompetence in sinoatrial disease

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Rate responsive pacing may be valuable in patients with chronotropic incompetence. A rapid, sensitive method of identifying which patients with sinoatrial disease have chronotropic incompetence would facilitate selection of patients that may benefit from implantation of rate responsive systems. This would have economic advantages. We gave isoprenaline in incremental doses up to 0·075 µg/kg/min to 14 patients with sinoatrial disease who had received AAIR systems. On repeated exercise testing with the Cleveland chronotropic adequacy exercise programme five showed chronotropic incompetence (maximum heart rate <115/min at peak exercise). In each case patients graded the peak exercise level as "hard" or above on the Borg exercise grading scale. The eight other subjects showed a sinus tachycardia at peak exercise of 130/min or above. All patients with chronotropic incompetence failed to show an acceleration of their heart rate in sinus rhythm in response to isoprenaline to a peak of 100/min (range <70–96). Two patients with chronotropic incompetence developed accelerated nodal rhythms and two remained paced at 30/minute throughout. The eight patients who showed chronotropic "competence" all developed a sinus tachycardia in response to isoprenaline (range 110–150/min). The difference in peak sinus rate in response to isoprenaline between the two groups was highly significant ($p < 0{\cdot}001$).

A peak rate in sinus rhythm <100/min in response to 0·075 µg/kg/minute of intravenous isoprenaline is a sensitive (100%) and specific (100%) marker of chronotropic incompetence in sinoatrial disease.

Method of head up tilt testing in the investigation of syncope

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Prolonged 60° head up tilt is gaining acceptance in the investigation of unexplained syncope, identifying the malignant vasovagal syndrome. Numerous protocols for tilting are in use but the most clinically useful is not yet defined. To try to do this several groups of patients and controls were tilted according to different protocols. Seventy one patients with unexplained recurrent syncope were tilted at 60° with a footplate support for a planned maximum of 60 minutes and 53 (75%) were syncopal at 24 (10) mins. A random 31 of these were tilted again and 24 (77%) were syncopal; a random 16 of these were tilted again and 13 (81%) were syncopal; a random 10 of these were tilted to 45% and only three (30%) were syncopal. Sixteen patients with syncope due to atrioventricular block were tilted and three (19%) were syncopal. Eighteen patients with syncope related to sinus node disease were tilted and two (11%) were syncopal. Twenty seven age matched non-syncopal controls were tilted and two (7%) were syncopal. A random 12 of these were tilted with a saddle support and seven (67%) were syncopal.

Reproducibility of tilt testing in patients with unexplained recurrent syncope is 80%. The rate of tilt syncope was significantly higher in patients with unexplained recurrent syncope than in controls or patients with syncope related to conduction tissue disease ($p < 0{\cdot}001$). Saddle tilt results in loss of specificity, tilting to less than 60° results in loss of sensitivity. Tilting should be for 45 minutes (mean time of syncope plus 2 SD).

Differential response of repolarisation to changes in ventricular loading in patients with abnormal wall motion

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Changes in ventricular loading conditions may influence the time course of repolarisation (and hence refractoriness). This study aims at examining a possible differential response in patients with abnormal wall motion compared with those with normal wall motion. We used the Valsalva manoeuvre to manipulate pressure and volume and recorded monophasic action potentials from the left ventricular endocardium as a measure of the time course of repolarisation during right atrial pacing. Twenty three patients were studied undergoing routine cardiac catheterisation for chest pain. Seven had neither angiographic evidence of abnormal wall motion nor a history of myocardial infarction (group 1); five had a history of myocardial infarction but normal wall motion (group 2); and 10 showed evidence of abnormal wall motion either with or without previous infarction (group 3). During the forced expiratory phase of the Valsalva manoeuvre venous return is impeded and systolic pressure falls. In group 1 systolic pressure fell from 138 (SD 31) mm Hg to a plateau of 97 (37) mm Hg ($p < 0{\cdot}02$). After release of the forced expiration during the rapid recovery phase it increased from 66 (26) mm Hg to 109 (32) mm Hg ($p < 0{\cdot}0001$). During the forced expiratory phase in group 1 monophasic action potential duration shortened from 311 (47) ms to 295 (47) ms ($p < 0{\cdot}001$) and lengthened during the rapid recovery phase from 285 (44) ms to 304 (44) ms ($p < 0{\cdot}0001$). Monophasic action potential changes in the opposite direction occurred in six of the 10 patients in group 3. An in between pattern was seen in the patients in group 2. It is unlikely that autonomic effects associated with the Valsalva manoeuvre would account for these findings.

Our results provide further evidence that changes in ventricular loading influence repolarisation in humans. With abnormal wall motion the effects on repolarisation were often opposite to those with normal wall motion. Regional differences in wall motion could by this mechanism generate local electrical gradients that may be relevant to the association of arrhythmia with impaired left ventricular function.

Pulmonary extraction and left atrial secretion of atrial natriuretic factor

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Atrial natriuretic factor (ANF) concentrations are similar in pulmonary arterial and systemic arterial samples, so it is thought that the lungs do not extract a significant amount of the peptide. We tested this hypothesis by measuring ANF concentrations in samples taken from multiple sites of the central circulation in 12 patients undergoing cardiac surgery. We also investigated the effects of cardiopulmonary bypass on ANF concentrations as any deficiency of the peptide could contribute to the risk of renal ischaemic injury. The mean age of the patients was 59 years (range 43–68), and there were three women. All patients had a history of angina, and five had had a previous myocardial infarction. The operation consisted of up to three vein grafts, either alone (three patients) or combined with an internal mammary artery graft (nine patients). Mean (SD) ANF concentrations were lower in pulmonary venous samples (41 (20) pg/ml) than pulmonary arterial samples (54 (18) pg/ml; $p < 0{\cdot}001$), showing 24% extraction of ANF by the lungs. Both left atrial (47 (23) pg/ml) and systemic arterial concentrations (52 (25) pg/ml) were higher than pulmonary venous concentrations ($p < 0{\cdot}05$), indicating secretion of ANF into the left side of the heart. Plasma ANF concentration fell from 68 (23) pg/ml before aortic crossclamping to 35 (13) pg/ml and 28 (9) pg/ml 10 and 30 minutes after the application of clamps respectively (both $p < 0{\cdot}005$). A rebound rise to 123 (33) pg/ml followed the release of the clamp ($p < 0{\cdot}001$).

We conclude that ANF is extracted in the lungs and that plasma concentrations are restored by direct secretion of the peptide into the left side of the heart. As ANF protects against renal ischaemic injury the considerable fall in plasma concentrations observed during cardiopulmonary bypass may contribute to this complication of cardiac surgery.

Cerebral blood flow autoregulation in complete heart block

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Patients with chronic complete heart block are known to have a reduced cerebral blood flow of up to 20% associated with a reduction in cardiac output of 30% despite a normal blood pressure. The time course of these changes is unknown, but they are reversed within a few minutes when VVI pacing at 70/min is started. We measured left and right carotid and vertebral artery flow in five patients (mean age 69 years) with a 7·5 MHz Doppler probe and Acuson 128 ultrasound machine. All patients had permanent pacemakers (four VVI one DDD) with no detectable underlying cardiac rhythm and were in VVI pacing at a heart rate of 70/min for at least one hour before being studied. None had evidence of carotid or vertebral artery stenoses. Patients were rested for 15 minutes before measurements were taken. After baseline readings heart rate was reduced to 40/min and measurements repeated after 15 minutes. Total cerebral blood flow fell by 3·3% (SD) 8·1%) when pacing rate was reduced to 40/min. Mean ratio of carotid to vertebral flow (total carotid flow ÷ total vertebral flow) was 3·6 (SE 0·94) at 70/min and 3·0 (SE 0·37) at 40/min (difference not significant).

There is no evidence of an acute change in cerebral blood flow, or its distribution, on reduction of heart rate from 70/min to 40/min during VVI pacing. This shows that cerebral autoregulation is well able to cope with sudden reductions in heart rate. The failure of autoregulation in complete heart block develops more gradually and is likely to be associated with a long term reduction of cardiac output.

Angiotensin converting enzyme inhibitors and magnesium conservation in patients with congestive cardiac failure

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Patients with congestive cardiac failure treated with long term diuretics are at risk from hypomagnesaemia.

Angiotensin converting enzyme inhibitors may attenuate diuretic induced hypomagnesaemia and therefore we investigated their effect on diuretic induced magnesium excretion in patients with congestive cardiac failure. Nineteen patients (group 1) taking diuretics alone (frusemide or bumetanide) were compared with 15 patients (group 2) taking diuretics plus either captopril or enalapril. Drug doses were stable for three months. Patients received an intravenous loading dose of magnesium sulphate (30 mmol/l) to minimise variability in baseline magnesium state after which urine was collected for 24 hours. The two groups were well matched for age, weight, and diuretic dose. Plasma magnesium concentrations were similar in the two groups (0·87 (0·02) and 0·86 (0·02) mmol/l). Twenty-four hour urine magnesium excretion was significantly lower in group 2 (18·5 (1·4) mmol/24(h) than in group 1 (26 0 (1·0) mmol/24(h) ($p < 0·0003$). Creatinine clearance was significantly lower in group 2 (49 (5·0) ml/min) than in group 1 (74 (5·9) ml/min) ($p < 0·002$). Creatinine clearance correlated strongly with magnesium excretion in group 2 ($p < 0·001$) but not in group 1.

The results suggest that angiotensin converting enzyme inhibitors have an important magnesium conserving effect. The likeliest mechanism is through a reduction in glomerular filtration rate, though their antialdosterone action may contribute.

Impaired left lower lobe ventilation: an isotope study of mechanisms

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We previously showed a significant correlation between cardiac enlargement and reduced left lower lobe ventilation on routine V/Q scanning. In a prospective study on 19 patients with large hearts a considerable improvement in left lower lobe ventilation was seen in the prone compared with the supine position. Although there was a similar change in normal volunteers, this was less noticeable. To elucidate the mechanism of this change 11 patients with enlarged hearts were studied, the change in the difference in signal at right compared with the left base being expressed as a ratio on passing from supine to prone. In those showing a reduction in ventilation at the left bases with inhaled krypton-81m the ratio on moving from supine to prone was 2·40 (0·46), representing a real increase at the left base (no changes were seen at the right base). No change was seen with intravenous ^{99m}Tc-MAA acting as a marker of lung position (0·96 (0·08) or in regional lung perfusion with intravenous ^{99m}Tc-MAA and the peak of the injected xenon-133 curve (1 1 (0·21)). There was also no change in ventilatory turnover, and thus no evidence of air trapping, from the injected xenon-133 washout curve (1 35 (0·71)). Combining the xenon washout and krypton data to produce an index of volume change produced a significant reduction at the left base (3·05 (1·7)). This suggests that the mechanism of the phenomenon may be due to lung compression and alveolar closure and that a change in position reverses this closure and thereby improves lung ventilation and gas exchange.

Effect of ischaemia on the relation between monophasic action potential duration and cycle length in the human left ventricle

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The duration of the monophasic action potential is shortened by both an increase in heart rate and ischaemia. Any protocol devised to study ischaemia is thereby complicated by the effect on the action potential duration of changes in cycle length. The aim of the study was to see whether it was possible to disassociate these two effects.

Left ventricular monophasic action potentials were recorded in 12 patients after routine coronary angiography during incremental; atrial pacing to their angina threshold or loss of 1:1 conduction. Each pacing rate was maintained for two minutes, thereby establishing steady state conditions. The monophasic action potential recording catheter was in a non-ischaemic area in six patients and in an ischaemic area in the other six patients, as shown by the use of isotope myocardial perfusion imaging. We observed a linear relation for steady state monophasic action potential duration—that is, for values obtained at the end of each two minute pacing train—between cycle lengths of 850 ms and 461 ms in both ischaemic ($r = 0·93$) and non-ischaemic regions ($r = 0·82$). The slope of the regression line for the ischaemic areas was greater than that for the non-ischaemic areas (28·6 ms *v* 23·5 ms per 100 ms cycle length decrease; $p < 0·05$). Rate correction algorithms such as the Bazett's formula are unreliable in non-steady state conditions but may be useful under steady state conditions when restitution is complete. Applying Bazett's formula to our data, we observed that changes in action potential duration in the ischaemic area showed a significant deviation from that in the non-ischaemic area, particularly at the shorter cycle lengths (288 ms *v* 312 ms at a cycle length of 500 ms; $p < 0·006$).

We conclude (*a*) that—ischaemia shifts the slope of the regression line relating action potential duration to cycle length while preserving the linear relationship and (*b*) that the rate correction algorithm applied to steady state values enables changes due to ischaemia to be differentiated from those due to changes in cycle length.

Effects of early captopril administration on left ventricular dilatation and function after acute myocardial infarction

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In a double blind study 99 patients (aged 40–75, 82 men) with acute myocardial infarction and a Norris score $>3·5$ were randomly assigned to receive captopril or placebo within 24 hours. Left ventricular (LV) volumes, ejection fraction, segment lengths, and cardiac output were measured serially by cross sectional and Doppler echocardiography. There were no differences in clinical and echocardiographic variables between the groups at baseline except for an excess of previous myocardial infarction in the placebo group (13/50 *v* 2/49; $p = 0·002$). By two months, compared with placebo, the captopril group had a lower LV systolic volume index (mean (SE) 45·6 (3·3) (ml/m^2 *v* 54·7 (2·8) ml/m^2, 95% confidence interval −17·8 to −0·6; $p = 0·04$) a higher LV ejection fraction (41·0 (2·1)% *v* 35·2 (1·7)%, 0·5 to 11·2; $p = 0·03$), and a shorter anterior segment length (87·3 (4·7) mm *v* 101·0 (3·6) mm, −25·7 to −1·8; $p = 0·02$). There was a non-significant trend towards a lower LV end diastolic volume index in the captopril group (75·7 (3·5) ml/m^2 *v* 83·6 (2·6) ml/m^2, −16·7 to 0·8; $p = 0·08$). No differences were identified in stroke volume index or cardiac index. In the placebo group there were significant increases in the anterior and posterior segment lengths from baseline to two months which did not occur in the captopril group.

This study provides further evidence that captopril can attenuate LV enlargement and improve LV function after myocardial infarction.

Continuous ST segment monitoring in the acute phase after admission to hospital with chest pain

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It has been reported that silent ischaemia occurring in unstable angina or after myocardial infarction is common and associated with an adverse short and medium term prognosis; most studies, however, have been carried out after stabilisation. To assess the frequency and prognostic implications of early ischaemic change in patients presenting with acute coronary syndromes we studied 248 patients (mean age 57) who presented to the accident and emergency department with chest pain assumed to be ischaemic in nature. Continuous electrocardiographic monitoring (CM5 + inferior lead) was started within six hours after admission with an FM recorder (mean 40 h, total 10 195 h). Strict criteria were used to define ischaemic change to avoid especially overdiagnosis on the basis of baseline ST segment elevation. Of the 248 patients, 99 (39%) had an acute myocardial infarction and 109 (43%) had unstable angina. During the 10 195 hours of taping 52 (21%) patients showed evidence of ischaemia during electrocardiographic monitoring and 29 (56%) had more than 60 minutes of ischaemia. At a mean follow up of 13 weeks (range 2–52) six out of 29 (20%) patients with more than 60 minutes of ischaemia had died and a further five (16%) had interventions (four coronary artery bypass grafting, one percutaneous transluminal coronary angioplasty). Of the 196 patients without ischaemia, six (3%) had died.

About a fifth of patients presenting with acute coronary syndromes have evidence of ischaemia in the acute phase. Continuous monitoring identifies a subgroup at significantly increased risk of an early unfavourable outcome. Early identification, investigation, and treatment of such a subgroup may improve their prognosis.

Collateral flow after acute myocardial infarction

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Left ventricular function is thought to improve after thrombolytic treatment in patients with myocardial infarction, but the mechanisms are not fully understood. Angiography was performed at 24 hours in 14 patients presenting with a first myocardial infarction who had been treated within three hours of onset of symptoms with anistreplase and heparin; treatment was repeated at 5–7 days in 10 of them. At the time of angiography myocardial flow was assessed by the xenon clearance technique. After intracoronary injection of xenon under direct vision scans were obtained with a mobile gammacamera fitted with a biplane collimator, which allows simultaneous acquisition in the 30° and 70° left anterior oblique projections. In four patients the infarct vessel was totally occluded at initial angiography; in one patient this was patent at 5–7 days and a further two patients developed totally occluded vessels. Ventricular function was unchanged (left ventricular ejection fraction 24·5% (5·5%) at 24 hours, 25 7% (5·1%) at

5–7 days) in the whole group, but in five of the six patients with occluded vessels and angiographically demonstrated collaterals left ventricular function tended to improve (23% (3·9%) to 27·3% (4·5%)). Xenon flow showed improved collateral flow from 43·1 (10·2) ml/100 g/min to 65·9 (11·4) ml/100 g/min and increased distribution to the left ventricle (14% (3%) to 21% (4%)) from the collaterals.

These results suggest that after myocardial infarction collateral flow tends to improve with time in patients with occluded vessels, and this may help to preserve ventricular function.

Prolonged anginal perceptual threshold in diabetes: effects on exercise capacity and myocardial ischaemia

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Anginal perceptual threshold (APT)—the time from onset of 0·1 mV ST depression to onset of angina during treadmill exercise—is prolonged in diabetes. We evaluated the functional importance of this perceptual abnormality by analysing its effect on exercise capacity and myocardial ischaemia in 32 diabetic patients and 36 non-diabetic controls. APT was prolonged in the patients by a mean of 86 s ($p < 0{\cdot}001$) and correlated closely with exercise capacity ($r = 0{\cdot}8$, $p < 0{\cdot}001$), although in the controls these variables were unrelated. In both groups the time to onset of electrical ischaemia was related to exercise capacity ($r = 0{\cdot}8$ and $0{\cdot}9$, $p < 0{\cdot}001$), but the slope of the regression was significantly flatter in the patients because APT was prolonged, allowing exercise to continue as ischaemia intensified. This permissive effect of prolonged APT on exercise capacity had unfavourable consequences as reflected by its correlation with ischaemia at peak exercise ($r = 0\ 6$, $p < 0{\cdot}001$)—the longer the threshold the greater the exercise capacity and the more severe the ischaemia. Indeed, the normal inverse relation between the severity of exertional ischaemia and exercise capacity seen in the non-diabetic controls ($r = 0{\cdot}4$, $p < 0{\cdot}02$) was completely lost in the diabetic group.

In conclusion, APT is a major determinant of exercise capacity in diabetes; prolongation has important functional consequences, depriving the patient of the signal to stop exercising as regional ischaemia intensifies. The effects of this process on arrhythmogenesis and myofibrillar damage remain to be determined.

Prognostic value of baroreflex testing early after myocardial infarction

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Baroreflex sensitivity (BRS) testing was performed in 99 patients 6–10 days after myocardial infarction with bolus doses of intravenous phenylephrine and intra-arterial monitoring (femoral or radial line). The mean rise in systolic blood pressure was 23 mm Hg and the mean dose of phenylephrine used on each injection was 0·8 mg. All patients tolerated the procedure well. The mean left ventricular fraction of the study group was 51·5% (14·8%), mean age was 56·4 (9·8) years, and the mean BRS was 7·06 (4·7) ms/mm Hg. BRS was inversely correlated with age ($r = -0\ 424$, $p < 0{\cdot}0001$) but not with ejection fraction or variability in heart rate. Infarct site or type (Q wave) had no significant effect on BRS. During follow up seven patients developed arrhythmic events (ventricular tachycardia or sudden death) and BRS in this group was considerably reduced (7·44 (4·65) *v* 1·38 (1·34); $p < 0{\cdot}002$). On 24 hour electrocardiographic analysis nine patients had non-sustained arrhythmias and BRS was again significantly reduced in this group (7·52 (4·65) *v* 3·6 (2·78); $p = 0{\cdot}018$). BRS was not significantly reduced when all cause cardiac mortality was analysed (7·3 (3·97) *v* 7·4 (4·65)).

In conclusion, BRS testing can be safely performed in the early period after infarction, is well tolerated, and gives important prognostic information on arrhythmic risk.

Exertional ST elevation after infarction: wall movement abnormality, reversible ischaemia, or both?

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Exertional ST elevation after myocardial infarction is a bad prognostic sign but its mechanism is obscure. We examined its relation to regional and global left ventricular wall movement and reversible ischaemia (angina or ST depression, or both) in 42 consecutive patients without previous infarction by echocardiography, radionuclide angiography (multiple gated acquisition), and symptom limited exercise testing. The 17 patients who developed ST elevation had lower regional (anterior: 2·1 *v* 6·0, $p < 0{\cdot}005$; inferior: 1·3 *v* 2·8, $p < 0{\cdot}01$) and global (10·1 *v* 13·4, $p < 0{\cdot}05$) wall movement scores. In 14 of these 17 patients with ST elevation the electrocardiographic location of ST elevation corresponded to underlying regional wall movement abnormalities (hypokinesia or dyskinesia, or both). Patients with ST elevation had lower radionuclide ejection fractions (33% *v* 47%, $p < 0{\cdot}04$) and shorter exercise duration (11·0 *v* 13·1 min, $p < 0{\cdot}03$) compared with the 25 patients without ST elevation. The frequency of reversible ischaemia was not significantly different between the two groups.

We conclude that exercise induced ST elevation after infarction is related to underlying left ventricular wall movement abnormalities and associated poor left ventricular performance but not with reversible ischaemia.

β-Endorphin release after acute myocardial ischaemia

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Plasma concentrations of β-endorphin (BE), an endogenous opioid peptide, increase in response to various stressful stimuli and are also raised in animal models of heart failure. In these models opioid antagonists improve cardiac performance, suggesting that BE may have a pathophysiological role. Plasma BE concentrations were measured serially in 55 patients (aged 37–75, 37 men) admitted to the coronary care unit with acute myocardial ischaemia. Myocardial infarction was confirmed in 42 patients, 31 (74%) of whom had at least one measurement outside the normal range of 2·5–7·2 pmol/l. The mean (SE) peak value for all patients with myocardial infarction was 22·3 (3·7) pmol/l, significantly higher than the peak value of 5·1 (1·0) pmol/l in the 13 patients with unstable angina (95% confidence interval (for difference of means) 9·4 to 24·9). The 12 patients with myocardial infarction who developed cardiac failure had a higher peak BE concentration than those without this complication (34·3 (8·3) *v* 17·4 (3·8) pmol/l, −32·8 to −0·9). Univariate analysis indicated significant correlations between peak BE concentration and creatine kinase activity and adrenocorticotrophic hormone, cortisol, and glucose concentrations. Although pain is a major stimulus to BE release, there was no difference in the pain scores of the patients with and without myocardial infarction (70(4) *v* 76(4), −19 to 6) or between patients with and without cardiac failure (79(11) *v* 72(4), −19 to 34).

BE is another component of the neuroendocrine activation associated with myocardial infarction and cardiac failure.

Can we predict which cardiac arrests outside hospital are ventricular fibrillation?

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Only an occasional patient with asystole outside hospital will survive, so extended trained ambulance staff should concentrate on ventricular fibrillation (VF). We analysed 1196 cardiac arrests in adults attended by extended trained staff in West Yorkshire to assess whether VF can be predicted. Fibrillation was the initial rhythm in 456 patients (38%); 64 survived to leave hospital. Only one of the remaining patients (585 asystole, 155 electromechanical dissociation) survived—an 18 year old patient with asthma who developed asystole in transit. Five factors were positively associated with VF: age less than 70 (predictive accuracy 43%), location of arrest in a public place (56%), arrest occurring in presence of paramedical staff (48%) or bystanders (42%), bystander resuscitation (58%), and response time shorter than six minutes (45%). When all five associated factors were present VF was found in 74% of the arrests; if none was present VF accounted for 9%. Fibrillation occurring after arrival of the ambulance or during transit was followed by 56·5% survival, but for those patients found in VF only a response time shorter than six minutes was associated with improved survival (14% *v* 5%).

Some factors are associated with VF, but their predictive value is not sufficient to be of much practical use.

Adrenaline, myocardial ischaemia, and ventricular arrhythmias in coronary heart disease

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Acute myocardial infarction is associated with striking activation of the sympathoadrenal system. We infused adrenaline and matching placebo in random order to achieve adrenaline concentrations in the range seen after acute myocardial infarction in 14 male patients (mean (SE) age 55 (2)) with stable angina. β-Blockers were witheld for at least 72 hous before the study. During adrenaline infusion (30 ng/kg/min) arterial adrenaline concentration increased from 70 (11) pg/ml to 579 (50) pg/ml, whereas during placebo infusion adrenaline concentration remained unchanged. No patient had ST segment depression at rest or during placebo infusion, but 11 of the 14 patients developed electrocardiographic evidence of myocardial ischaemia during adrenaline infusion (⩾1 mm horizontal or downsloping ST segment depression), although the increases in heart rate (67 (3) to 81 (2) beats/min) and systolic blood pressure (141 (7) to 146 (6) mm Hg) were modest. Ventricular arrhythmias developed or became more frequent or more complex during adrenaline infusion in five of the 14 patients, but ventricular tachycardia was not observed and no patient required specific antiarrhythmic treatment. During the control period supine bicycle exercise (load 26 (3) W) in 11 patients resulted in ⩾1 mm ST segment depression in five. Mean ST segment depression was similar during control exercise and during adrenaline infusion at rest (0·8 (0·1) mm and 1·1 (0·2) mm respectively). Ten patients undertook exercise during adrenaline infusion, of whom eight developed ⩾1 mm ST segment depression. Mean ST segment depression (1·8 (0·4) (mm) was greater than during the control exercise period ($p < 0·05$).

Thus adrenaline concentrations of the order seen after acute myocardial infarction are associated with potentially deleterious effects in patients with stable coronary heart disease. Endogenous adrenaline may contribute to myocardial ischaemia and the development of ventricular arrhythmias during acute myocardial infarction.

Reactivity of eccentric and concentric coronary stenoses in chronic stable angina

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Eccentric coronary stenoses are generally thought to be capable of changing their calibre in response to constrictor and dilator stimuli thus leading to a variable anginal threshold in patients with chronic stable angina. On the other hand, concentric stenoses are believed not to react in a similar manner. In 44 patients (34 men, 10 women age 55 (11) years) with chronic stable angina and angiographically documented coronary artery disease (⩾50% coronary luminal diameter reduction) we studied the response of 55 coronary stenoses (50–90% diameter reduction) to the administration of 1 mg intracoronary isosorbide dinitrate (54 stenoses) and intravenous ergometrine (12 stenoses). Computed quantitative angiography was used to assess the degree of eccentricity of each stenosis and to measure the coronary diameter of reference segments (angiographically normal segments proximal to the stenosis) and stenotic segments during baseline and after isosorbide dinitrate and metrine. Twenty six of the 55 stenoses were eccentric (47%) and 29 (53%) concentric. After isosorbide dinitrate coronary stenosis diameter increased ⩾10%, compared with baseline, in 18 of the 26 (69%) eccentric stenoses and in 11 of the 29 (38%) concentric stenoses ($p < 0·05$). Mean diameter of eccentric stenoses increased from 1·11 (0 25) mm during baseline to 1·32 (0·32) mm after isosorbide dinitrate (19% (14%) increment), whereas diameter of concentric stenoses changed from 1·10 (0·37) mm to 1·19 (0·38) mm (10% (15)%) increment) ($p < 0{\cdot}05$). Average dilatation of reference segments was not significantly different in patients with concentric and eccentric stenoses (7% (15%) and 10% (14%) respectively). Ergometrine, which did not produce angina or ST segment shifts in any patient, reduced stenosis diameter by $\geqslant 10\%$ in four out of five eccentric stenoses (mean diameter reduction = 17 (9)%) and in four out of seven concentric stenoses (mean reduction = 12 (10)%) (NS). Constriction of reference segments with ergometrine was similar in patients with eccentric and concentric stenoses (11 (8)% and 12 (7)% respectively).

Thus, in patients with chronic stable angina eccentric stenoses have a significantly larger ability to dilate in response to isosorbide dinitrate than concentric stenoses. Although a significantly larger proportion of eccentric stenoses have the potential for dynamic changes of calibre, however, a sizeable proportion of concentric stenoses also have this potential.

Time course of ultrastructural injury and repair to pulmonary capillaries after experimental unilateral lung transplantation

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A donor lung is injured during preservation and is generally thought to be injured by reperfusion. Donor lungs from rats preserved by flush perfusion with cold Marshall's solution at 4°C were examined by electronmicroscopy after two, four, or seven hours' storage at 4°C and after transplantation (syngeneic) at four or 12 hours (six animals per time interval). During preservation rapid capillary remodelling occurred. Both endothelial and epithelial components of the blood-gas barrier thinned (surface to volume ratio increased by two hours; $p < 0{\cdot}001$). Pericapillary oedema developed involving the blood-gas barrier when basement membrane thickness increased significantly ($p < 0{\cdot}001$). Occasional breakage of the endothelial cell sheet occurred after four hours' preservation. Even after seven hours' preservation there was no evidence of irreversible cell damage. After transplantation type I and type II pneumonocytes recovered after 12 hours. Endothelial cell cytoskeletal remodelling took longer. Oedema decreased rapidly during the first four hours, despite the number of adherent neutrophils increasing threefold. Findings were similar in the allogeneic transplanted dog lung.

Thus the pulmonary capillaries of transplanted lungs showed no structural evidence of reperfusion injury; rather a gradual resolution of the changes incurred during preservation injury.

Fatal complications as a result of underestimated coronary artery disease at the time of corrective cardiac surgery

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Data from 321 postmortem reports (between 1970 and 1989) were analysed to obtain information about the fatal complications after open heart surgery in adults. The indications for surgery were: valve disease ($n = 203$, (group I); ischaemic heart disease ($n = 86$, (group II); combination of the two ($n = 30$, (group III), and miscellaneous ($n = 2$, (group IV). In all, 147 patients (46%) died within 24 hours of operation and 128 (40%) between one and 30 days after operation, and there were 46 (14%) late deaths. The main cause of death was cardiac in origin in 204 cases (63%), thoracic bleeding in 28 cases (9%), other organ complication in 45 cases (14%) and multiorgan failure in 44 cases (14%). The most frequent pathological finding was myocardial infarction or signs of subendocardial injury ($n = 158$). In the ischaemic groups (II and III; cardiac deaths $n = 90$) it was the result of incomplete myocardial revascularisation in 25 cases (27%). In the non-ischaemic groups (I and IV; cardiac deaths $n = 114$) in 36 cases (32%) it was as a consequence of unidentified coexisting coronary artery disease.

These data suggest that all adults should have complete visualisation of their coronary artery tree at the time of preoperative investigations and in case of existing coronary artery disease they should undergo complete myocardial revascularisation in addition to corrective cardiac operation.

Warm cardioplegic induction improves rate of recovery of myocardial function after prolonged storage for transplantation

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Cooling blood has detrimental effects on its perfusion characteristics. During the early moments of cold cardioplegic infusion the crystalloid solution cools the residual blood in the coronary vasculature, which may adversely affect the distribution of the cardioplegic solution. To investigate whether such an effect jeopardises myocardial preservation for transplantation cardioplegic induction was performed in rat hearts infused (60 mm Hg) with St Thomas's Hospital cardioplegic solution. Two infusion conditions were studied: (*a*) one minute infusion at 22–24°C followed by two minutes at 7.5°C and (*b*) three minutes at 7·5°C. For each condition three groups of hearts (six/group) were studied after 0, four, and eight hours of storage at 7·5°C after which they were heterotopically transplanted into the abdomen of recipient rats. With implanted fluid filled intraventricular balloons cardiac function was assessed by constructing pressure-volume curves one, four and 24 hours after transplantation. The groups with the initial warm infusion accepted a greater volume of cardioplegic solution than the cold groups (29 (1·7) ml *v* 22·3 (1·6) ml $p < 0{\cdot}05$). After one hour of reperfusion the recovery of heart rate was poor in all six groups (NS between groups), but precontrol values were attained by 24 hours. In the eight hour storage groups the recovery of systolic pressure (measured at 90 µl balloon volume) recorded one hour after reperfusion was significantly better in the warm than the cold infusion groups (111·3 (7·5) *v* 87·4 (6·4) mm Hg; $p < 0{\cdot}05$), so too were diastolic (11·2 (0·9) *v* 20·0 (5·6) mm Hg; $p < 0{\cdot}05$) and developed pressures (100·2 (7·2) *v* 69·3 (7·2) mm Hg; $p < 0{\cdot}05$). After four hours reperfusion these differences in function were still apparent (91·7 (9·2) *v* 73·6 (5·3) mm Hg, 14·7 (1·3) *v* 23·7 (4·8) mm Hg, and 77·0 (8·7)

v 50·4 (5·9) mm Hg for systolic, diastolic, and developed pressures respectively; $p < 0·05$), but after 24 hrs of reperfusion there was no longer any difference in function between the groups (119·3 (8·0) v110·4 (7·4) mm Hg, 21·3(5·7) v 24·0 (4·4) mm Hg, 98·0 (9·0) v 86·4 (8·4) for systolic, diastolic, and developed pressures respectively; NS). There were no differences in systolic, developed, or diastolic pressures between the warm and cold groups stored for 0 and four hours; (NS all parameters).

In conclusion, warm cardioplegic induction improves the rate, but not the ultimate extent, of myocardial functional recovery after prolonged storage for transplantation.

Growth pattern of paediatric hearts after transplantation

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Growth pattern of the heart structures after paediatric transplantation is of great interest. To evaluate the possibility of cardiac growth after cardiac transplantation 29 patients followed up for a minimum period of 18 months were studied by serial echocardiography. The recipients' and donors' mean age at time of transplantation was 9 (0·5–16) years and 12 (2·5–35) years respectively. All patients were treated with cyclosporin and azathioprine without the routine use of steroids. Echocardiographic assessment was performed at intervals of three months after transplantation. Patients' weight increased from 40 (SD 11·6) kg to 49 8 (15·3) kg during the period of follow up, ranging from 18 to 72 (mean 48) months. Left ventricular dimensions in diastole and systole, left ventricular posterior wall thickness and mass, and aortic root diameter were measured and plotted against body weight. Growth patterns of cardiac dimensions in each patient were compared with published growth patterns in normal children. The initial left ventricular dimension in diastole was 39·8 (3·9) mm or 94·3% (9 1%) of predicted. At last examination left ventricular dimension in diastole was 41·5 (4·3 mm) or 93·8% (18·3%) of predicted.

It is concluded that paediatric cardiac allografts are capable of growth. This includes cavity dimensions, left ventricular mass, and aortic root diameter. The rate of growth of the different structures is variable and may be influenced by the discrepancy in size between donor and recipient, as well as blood pressure. Longer periods of follow up are required to define the full growth potential of the transplanted paediatric heart.

Controlled trial of physical training in chronic heart failure

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In a controlled trial of eight weeks duration home-based bicycle exercise training in patients with moderate to severe chronic heart failure (mean age 61·8 (1·5), left ventricular ejection fraction 0·20 (0·02) exercise duration and peak oxygen uptake were increased by about 20%. Exercise heart rate and rate × pressure product and 24 hour ambulatory heart rate and blood pressure were all significantly reduced, consistent with reduced myocardial oxygen requirement. Variability in heart rate was increased and resting noradrenaline spillover was reduced, both suggesting a reduced sympathetic to parasympathetic autonomic balance after training. Training increased cardiac output at rest and on exercise primarily owing to an increase in stroke volume, with systemic vasodilatation. The increase in exercise tolerance after training was closely linked to compliance with the training programme, indicating the specificity of the response.

These results suggest that carefully selected patients with moderate to severe heart failure can achieve significant and worthwhile improvements with exercise training and support the hypothesis that physical deconditioning may be partly responsible for some of the associated abnormalities and exercise limitation in chronic heart failure. They refute the frequent but unsupported recommendations that regular exercise should be avoided in chronic heart failure.

Inspiratory muscle fatigue and limitation of exercise by dyspnoea in chronic heart failure

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The mechanisms limiting exercise capacity in chronic left heart failure (CHF) are not known, and it seems that dyspnoea does not simply relate to increased pulmonary wedge pressure. Fatigue of the respiratory muscles has been described in chronic lung disease and might contribute to dyspnoea in CHF. We evaluated respiratory muscle function in CHF with a novel non-invasive index of inspiratory muscle fatigue (SR-τ_{mo}). Peak transdiaphragmatic pressure and relaxation rate (τ_{di}) during nasal sniffs are accepted indices of respiratory muscle fatigue, but their measurement requires gastric and oesophageal intubation. The time constant of pressure relaxation during gasps through a Starling resistor (SR-τ_{mo}) was compared with standard nasal sniffs in normal subjects at rest and during fatigue; gasp SR-τ_{mo} correlated well with sniff τ_{di} ($R = 0·76$, $p < 0·02$). Ten patients with CHF (New York Heart Association grade III) and 10 age matched controls performed maximal symptom limited treadmill exercise. Maximum inspiratory pressure (MIP), maximum expiratory pressure (MEP), SR-τ_{mo}, and maximum hand grip strength were recorded. At peak exercise MIP and MEP decreased significantly in the patients with CHF but not in the controls ($p < 0·01$), SR-τ_{mo} became prolonged at peak exercise in the patients but not in the controls ($p < 0·02$) and hand grip did not change significantly with exercise in either group.

These data provide evidence of respiratory muscle weakness and fatigue in CHF when exercise is limited by dyspnoea whereas the strength of non-exercising muscle (hand grip) is not reduced. These changes are not seen in normal subjects and might contribute to the limitation of exercise capacity in CHF.

Interlead QT variability as a measure of temporal dispersion of ventricular recovery

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A simple non-invasive measure of time dispersion of ventricular recovery would be of great clinical importance. Increased dispersion is thought to be an important basis for ventricular arrhythmias, and a decrease in dispersion probably explains the action of class III antiarrhythmic drugs. QT interlead variability (dispersion) on the surface electrocardiogram may have potential as a measure of time dispersion of ventricular recovery. To examine this hypothesis QT dispersion was measured in three groups of patients. Each study entailed a situation in which dispersion of recovery time was expected to be minimal and one in which dispersion was expected to be large. In patients randomised to treatment with placebo or sotalol after myocardial infarction QTc dispersion (calculated as maximum QTc − minimum QTc) was significantly less in those receiving sotalol. In patients with a long QT interval associated with a history of ventricular arrhythmia (arrhythmogenic QT prolongation) QT dispersion was significantly greater than that in patients in whom a long QT was due to sotalol (antiarrhythmic QT prolongation). In patients with normal hearts QT dispersion was significantly less in sinus beats that with ventricular extrasystoles.

Thus all three studies provide strong support for the hypothesis that interlead QT variability reflects temporal dispersion of ventricular recovery.

The calcium release channel from cardiac sarcoplasmic reticulum. Characterisation of the channel from human hearts and its function in acute ischaemic injury

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The release of calcium from the sarcoplasmic reticulum (SR) is central to excitation-contraction coupling. In previous animal experiments the physiological release pathway has been identified as a calcium permeable ion channel in the SR membrane. In this study purified SR membrane vesicles were isolated from human hearts and, by fusing these vesicles with artificial planar phospholipid bilayers, single channel recordings were obtained under voltage-clamp conditions. The results provide the first report of the calcium release channel from human tissue and suggest that the channel is similar to that reported in other species. In addition, altered channel function does not seem to contribute to the impairment of calcium release in SR in end stage cardiac failure. Experiments also performed to investigate the effects of acute ischaemia on the calcium release channel from sheep hearts show that the channel is a target for early degradation during ischaemia. The effects of proteolysis and exposure to free radicals in vitro provide evidence that degradation of the channel leads to a phase of increased opening followed by loss of function.

These results suggest that damage to the calcium release channel may contribute to myocardial stunning.

Excess insulin secretion: a powerful new predictor of myocardial infarction of particular importance in Asians

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Increased insulin concentrations have been found in survivors of myocardial infarction, and in some prospective studies insulin has predicted subsequent cardiac events, but its independent role and mechanism of action are unclear. Insulin and C peptide are secreted by the pancreas in equimolar concentrations, insulin being subject to considerable first pass removal by the liver and C peptide being unaffected. The association between these peptides and the relative risk of myocardial infarction were examined in 150 consecutive male survivors of first infarction and in controls marked for age and ethnic origin. The subjects were either white ($n = 76$) or Asian ($n = 74$), the Asians having an excess rate of ischaemic heart disease and diabetes. Higher concentrations of C peptide ($p < 0{\cdot}0001$) and triglyceride (Tg) ($p < 0{\cdot}01$) and lower concentrations of high density lipoprotein cholesterol (HDL) ($p < 0{\cdot}001$) were found in the patients. In a multivariate analysis the C peptide concentration and cholesterol/HDL ratio emerged as the most powerful independent predictors of cases in both ethnic groups. The C peptide concentration was independently associated with Tg concentration ($p < 0{\cdot}001$), which itself was associated closely with the cholesterol/HDL ratio ($p < 0{\cdot}0001$).

These data suggest that the cluster of risk factors that include high insulin secretion, high Tg concentration, and low HDL concentration may be important to the development of coronary artery disease (CAD). As established risk factors for CAD are lower in Asians, C peptide, a new marker of risk of myocardial infarction, which was higher in Asian than in white subjects, may explain both the excess of CAD and diabetes in Asian people.

The heart after direct current countershock: a novel myocardial syndrome?

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The mechanisms of myocardial injury after direct current countershocks from a hospital defibrillator were investigated in adult greyhounds. At one minute after five transthoracic shocks (400 J, damped sine wave, 0·5 minutes interval) lactate production occurred (mean lactate extraction −193 (SE 135)%) and mean peak noradrenaline concentration in coronary sinus blood was 916 (313) pg/ml. Coronary sinus oxygen saturation rose from 42 (4)% to 63 (2)% and mean global left ventricular myocardial blood flow rose from 156·9 (18·7) ml/minute to a peak value of 221 0 (38·7) ml/minute after five shocks. Glutamate-, but not succinate-supported, oxidative phosphorylation in mitochondria isolated from hearts after five lethal shocks was significantly lower than that in controls (50·7 (4·9) nanoAtoms oxygen (nAO) mg mitochondria/minute *v* 86·6 (13 6) nAO/mg/minute, $p < 0{\cdot}02$). Free radicals of the peroxyl group were detected in heart tissue by electron spin resonance spectroscopy after two internal shocks (50 J), although there was no rise in coronary sinus malondialdehyde concentrations in the dogs after five transthoracic shocks. Though a dramatic rise in noradrenaline concentration was observed in coronary sinus blood after five shocks, there was no accompanying rise in neuropeptide Y concentration,

It is proposed that this combination of physiological changes, comprising reduction of oxygen utilisation, production of lactate, mitochondrial depression, free radical generation, and increased blood flow with a rise in coronary sinus noradrenaline but not in neuropeptide concentration are characteristic of the heart after direct current countershock.

Equivalent efficacy of single bolus and infusion dosing of recombinant tissue plasminogen activator in a canine model of coronary artery thrombotic occlusion and reperfusion

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In the treatment of acute myocardial infarction thrombolysis is now accepted as being of value in salvaging ischaemic myocardium and reducing mortality. Recent clinical evidence has suggested equivalent efficacy in terms of early coronary patency with bolus dosing of recombinant tissue plasminogen activator (rt-PA) compared with infusion dosing. The aim of this study was to evaluate the utility of single bolus administration of rt-PA compared with an infusion. Anaesthetised dogs were subjected to 90 minute's thrombotic occlusion of the left anterior descending coronary artery (LAD) after introduction of a copper coil on a guide wire. rt-PA (Duteplase, Wellcome Foundation) was administered at the same dose (0·6 MIU/kg) over six minutes (group 1, $n = 8$) or 60 minutes (group 2, $n = 8$). LAD patency was assessed arteriographically and microvascular coronary flow by radiolabelled microspheres. Infarct size was determined histochemically after 120 minutes of reperfusion and plasma fibrinogen monitored throughout. LAD patency was restored in 43·1 (7·0) min and 42·9 (7·4) min in groups 1 and 2 respectively. Patency after 60 minutes was 88% for both groups. Subendocardial microvascular coronary flow was restored to 102·6% (27·8%) and 114·3% (9·4%) (of control) in groups 1 and 2 respectively. There was no significant difference in infarct size expressed as percentage of area of risk (group 1, 42·1% (9·1%); group 2, 46·3% (8·4%)) or in circulating fibrinogen concentrations.

Thus, in an anaesthetised dog model of coronary arterial thrombotic occlusion and reperfusion single bolus administration of rt-PA achieves equivalent efficacy (LAD patency and microvascular coronary flow) to infusion dosing.

Free radical activity at the time of successful thrombolysis: relation to left ventricular function

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Although thrombolytic treatment of acute myocardial infarction often restores coronary patency and improves prognosis, improvement in left ventricular function is small. Experimental data suggest that residual impairment of left ventricular function after successful thrombolysis is due to reperfusion injury involving free radicals, as well as to damage accrued during ischaemia, but there is no clinical data on this point. In 50 patients given streptokinase for myocardial infarction peripheral venous blood samples before streptokinase and two hours later were centrifuged and frozen for assay of a marker of free radical activity: thiobarbituric acid reactive material (TBA-RM) reflects lipid peroxidation by free radicals. Coronary arteriography was performed within 72 hours of thrombolysis to determine coronary patency. The infarct related artery was patent in 42 (84%) patients and occluded (TIMI grade 0 or 1) in eight. In the 42 with a patent artery the concentration of TBA-RM increased after streptokinase by 105 (96) nmoles/g/albumin, whereas in the eight with an occluded artery TBA concentration decreased by 147 (80) ($p < 0{\cdot}01$ between groups). In those with a patent artery there was a weak correlation between the rise in TBA-RM and left ventricular ejection fraction ($R = -0{\cdot}3$, $p < 0{\cdot}02$).

These data show that at the time of successful thrombolysis there is an increase in lipid peroxidation, which is not seen in patients in whom the artery remains occluded. This is the first demonstration in humans of free radical activity associated with documented myocardial reperfusion and provides indirect evidence of reperfusion injury, supported by the association between a large rise in TBA-RM concentration and low left ventricular ejection fraction.

Prediction of arrhythmic events in patients after infarction by heart rate variability and signal averaged electrocardiogram

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A total of 387 consecutive patients admitted with an acute myocardial infarction were assessed before discharge. Holter recordings were analysed for ventricular ectopic frequency > 10/h (VE) and heart rate variability. Signal averaged electrocardiograms were analysed for late potentials. Clinical data and left ventricular ejection fraction were also recorded. Mean age was 59·2 (10·6), ejection fraction 50·43 (14·9), and heart rate variability 27·6 (11·4). Late potentials were present in 79 of the 387 patients and VE in 49 of the 387 patients. During follow up 20 patients had arrhythmic events, including sudden death or sustained ventricular tachycardia. These patients had reduced heart rate variability (16·2 (6·9) *v* 27·75 (11·2); $p < 0{\cdot}0001$) and ejection fraction (40·7 (15·4) *v* 50·9% (14·8%); $p < 0{\cdot}001$). Stepwise multivariant analysis showed that heart rate variability followed by VE, late potentials, and Killip class were independent predictors of arrhythmic events, whereas ejection fraction, age, infarct site, and Q waves were not. Heart rate variability was only weakly correlated with age ($r = -0{\cdot}19$; $p < 0{\cdot}001$) and ejection fraction ($r = 0{\cdot}27$; $p < 0{\cdot}001$). Whereas reduced heart rate variability (< 20) was the most sensitive predictor of arrhythmic events (17/20), the positive predictive accuracy was 15·2% (17/112 patients). A combination of heart rate variability and late potentials yielded a higher positive predictive accuracy (32·4% (12/37 patients)) than any other combination.

In conclusion, a combination of heart rate variability and late potentials identifies a small subgroup of patients at high risk of arrhythmic events after acute myocardial infarction. These tests offer a simple non-invasive method of risk stratification independent of ejection fraction and can be obtained from a single ambulatory electrocardiogram.

Early coronary bypass surgery after acute myocardial infarction

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This is a randomised study of patients (men or women ≤65) surviving acute myocardial infarction and having a positive exercise test before discharge. The aim was to evaluate the effect of coronary bypass surgery on mortality. Those with a positive exercise test were considered for coronary angiography and for inclusion in the study when (*a*) left ventricular ejection fraction was >30% and (*b*) one coronary artery was narrowed by >70% and not supplying a dyskinetic ventricular segment. Patients randomised to surgery were operated on as soon as possible. Follow up was five years. All patients meeting clinical criteria but otherwise excluded were registered, and information on survival was obtained at two years. In all, 4658 patients were assessed and 3334 (71%) had an exercise test. This was positive in 728 (22%) and 598 had coronary angiography. Seventy patients did not wish to take part and 18 had severe angina requiring intervention. A total of 348 were randomised. Baseline characteristics of each treated group were similar. At two years the survival in the medical group was 96% and in the surgical group 93%. At five years the figures were 88% and 91%. Thirty patients in the medical group required surgery within five years. In those patients with a negative exercise test the two year mortality was 8%, with 8% requiring coronary bypass surgery.

Thus, a negative exercise test does not allow complacency whereas a positive exercise test does not imply that surgery is inevitable.

Cardiac catheterisation 1988–9: the RITA trial coronary arteriogram register

RITA Trial Steering Committee

The Randomised Intervention Treatment of Angina (RITA) trial compares the long term effect of coronary bypass surgery and coronary angioplasty in patients treatable by either procedure. In addition, a register of patients undergoing cardiac catheterisation is maintained in the RITA trial centres to assess the overall context of patient recruitment. The first 21 months of register forms (21 881 patients) have been analysed. Cardiac catheterisation was performed during day case (14%), overnight (24%), or longer (62%) hospital admission. Reasons for investigation were angina (69%), myocardial infarction (10%), and valvar or other cardiac disease (21%). In patients with angina coronary arteriography showed single vessel disease in 20%, two vessel disease in 22%, and more extensive coronary disease in 41%. The planned management of patients with angina included elective coronary surgery (39%), elective coronary angioplasty (12%), or RITA randomisation (3%), but in 42% revascularisation was considered to be unnecessary. Disease in more than three major coronary vessels (5%), left main stem disease (4%), unsuitable coronary anatomy (33%), and a fatal complication of coronary arteriography (0·1%) were all criteria for exclusion from RITA. Randomisation was refused by 2% of patients with angina and by the referring physician in 3% of cases.

The RITA coronary arteriogram register has produced important information abut current British cardiac practice. Around half of the patients catheterised for angina at RITA centres were referred for a revascularisation procedure, of whom 27% were suitable for coronary angioplasty.

Does epidural neurostimulation have an anti-ischaemic as well as analgesic effect in patients with angina?

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We studied 11 patients with epidural neurostimulators implanted for intractable severe angina to determine whether epidural stimulation reduces myocardial ischaemia as well as relieves pain. All patients showed improvement in symptoms. Right atrial pacing and treadmill exercise testing were performed with the neurostimulator off, on, and off. The main results (mean (confidence interval)) are comparing off and on. With right atrial pacing, maximum pacing rate increased from (143 (9·5) to 150 (6·7) beats/min; $p < 0{\cdot}02$); total ST segment depression at 90% maximum control (off) was reduced from 6·4 (4·0) to 5·2 (3·3) mm ($p < 0{\cdot}02$), and at rates of 120, 130, and 150 beats/min ($p < 0{\cdot}05$). Maximum RPP was not significantly different despite higher heart rate (HR) because of a fall in maximum systolic blood pressure (135 (14) to 124 (12) mm Hg; $p < 0{\cdot}05$) during stimulation. With exercise testing ($n = 9$) exercise duration was increased from 445 (156) to 507 (163) ($p < 0{\cdot}05$); total ST segment depression at peak exercise was less, 5·6 (3·6) to 3·9 (3·3) mm ($p < 0{\cdot}01$) and at 90% maximum control (off) HR, (3 7 (3·0) to 2·8 (3·5) mm; $p < 0{\cdot}01$). Maximum RPP was not significantly different despite increased work and HR.

These results indicate that epidural neurostimulation increases exercise duration and time to angina (right atrial pacing) with less ST segment depression at comparable RPP and therefore has an anti-ischaemic effect, which may in part be due to peripheral vasodilatation reducing cardiac work.

Critical aortic stenosis diagnosed prenatally

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Of over 450 structural cardiac abnormalities detected antenatally, critical aortic stenosis was diagnosed in 26 cases at presentation. The cardinal sign on the echocardiogram common to all cases was a poorly contracting left ventricle. Other features, often present but not consistent, included cardiac enlargement, aortic hypoplasia, restricted mitral excursion, an intact atrial septum, increased myocardial echogenicity, and abnormal aortic Doppler flow. Eight fetuses showed evidence of intrauterine cardiac failure. Sequential echocardiographic studies in three cases showed reduced or no growth of the mitral valve orifice, aortic valve size, and left ventricular dimensions so that these measurements became smaller for gestational age as pregnancy progressed. This observation was also noted in four fetuses in whom there was a time delay between the scan and postmortem examination. Pregnancy was terminated in 13 patients. One fetus is not yet delivered, but of the remaining 12 continuing pregnancies there are no survivors. There were two spontaneous intrauterine deaths and 10 neonatal deaths, six of which occurred on the first day of life. The diagnosis was confirmed in 22 cases at postmortem examination and in a further case at cardiac catheterisation.

Critical aortic stenosis diagnosed prenatally includes a range of abnormalities, with some cases progressing to the hypoplastic left heart syndrome with advancing gestational age. This would account for the poor outcome in our series and the discrepancy between the prenatal and postnatal incidence.

Transoesophageal echocardiography (TOE) in children with congenital heart disease

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TOE with a dedicated single plane paediatric probe was performed prospectively in 57 anaesthetised children before either cardiac catheterisation or cardiac surgery to evaluate the potential of this new technique in (*a*) the initial diagnosis, (*b*) perioperative management, and (*c*) the postoperative follow up of children with congenital heart disease. Age at study ranged from 9 months to 14·8 years (mean 5·6 years) and body weight from 4·7 kg to 52 kg (mean 19·7 kg); 38 children weighed less than 20 kg. All studies were successful; no complications were encountered. The TOE findings (imaging, pulsed Doppler, colour flow mapping) were correlated with the results of previous precordial studies and cardiac catheterisation or surgical inspection, or both. TOE consistently provided more detailed insights into the morphology and function of systemic and pulmonary venous return, both atria, the intra-atrial septum, Mustard baffles, both atrioventricular valves and their subvalvar apparatus, and the left ventricular outflow tract. Additional information was obtained in 31 of the 57 (54%) patients. Follow up studies after atrioventricular valve repair or replacement, or both, and after a Mustard or Fontan procedure were particularly rewarding. During aortic valve valvuloplasties TOE permitted the immediate exclusion of aortic regurgitation and monitoring of ventricular function. Intraoperative TOE was a valuable complementary technique to epicardial ultrasonography as it allowed the continuous monitoring of ventricular function and volume state immediately after bypass surgery. Problem areas for single plane TOE visualisation were the apical interventricular septum, the right ventricular outflow tract, and the left pulmonary artery. This experience suggests that the main indications for TOE studies in children are (*a*) specific atrial or atrioventricular junction lesions, (*b*) in perioperative monitoring, and (*c*) in the late follow up of atrial baffle procedures, Fontan procedures, and atrioventricular valve repair or replacement, or both.

In anaesthetised children with congenital heart disease TOE is an important and safe diagnostic and perioperative monitoring technique. It complements precordial studies, providing more detailed information on specific lesions and cardiac function in many instances.

Doppler echocardiographic detection of anthracycline induced changes in diastolic ventricular function in children

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Anthracycline drugs produce dose dependent myocardial damage—monitoring their incremental effect on ventricular performance provides a model for comparison of ventricular function assessment techniques. Preliminary results from a serial Doppler echocardiographic study are presented. Ninety Doppler echocardiographic examinations were performed in 51 patients aged 5 months to 22 years between one and five times each who had received 0 (pretreatment) to 580 mg/m^2 anthracyclines. Left ventricular ejection fraction was calculated from M mode dimensions. Peak early (e) and late (a) transmitral flow velocities were measured by pulsed wave Doppler sampling at the mitral valve leaflet tips and the ratio of e to a was calculated. Patients were divided into a pretreatment group and five groups of 100 mg/m^2 dose increments. Mean left ventricular ejection fraction was 72–73% in all groups except that receiving >400 mg/m^2, in which it was 67% ($p = 0{\cdot}015$). There was a biphasic trend of e/a ratio with dose. The initial mean (SD) in the pretreatment group ($n = 16$) was 1·73 (0·4), falling to 1·42 (0·3) by 100 mg/m^2 ($n = 11$), $p = 0{\cdot}02$; the 35 patients receiving <200 mg/m^2 had a ratio of e/a of 1·37 (0·03) and those receiving >200 mg/m^2 ($n = 39$) a ratio of 1·49 (0·3) ($p = 0{\cdot}04$), with a peak of 1·54 (0·2) at 300–400 mg/m^2 falling to 1·46 (0·3) at higher doses.

Anthracycline treatment produces changes in left ventricular diastolic filling patterns detectable by Doppler echocardiography before abnormalities of systolic function occur. Further serial echocardiographic studies of this model of progressive ventricular dysfunction are indicated.

Comparative values of intraoperative transoesophageal and epicardial ultrasonography in surgery for congenital heart disease

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Both intraoperative transoesophageal (TOE) and epicardial (EPI) ultrasonography (two dimensional imaging, colour flow mapping, and spectral Doppler) were attempted in 26 patients undergoing intracardiac correction for congenital heart disease to determine the relative advantages and limitations of either technique in assessing both the underlying morphology and the immediate surgical results. Introduction of the TOE probe was successful in 24 patients (92%). TOE studies were restricted to studies before bypass alone in nine children who were intubated with an uncuffed endotracheal tube. Twelve patients were studied before and after bypass and three patients were studied after bypass alone. In a 4·7 kg infant introduction of the probe raised ventilation pressures dramatically and required anaesthetic management. No other complications were encountered during TOE. Complete EPI studies were performed in all patients without complications. The assessment of the intracardiac morphology before bypass was more complete with EPI. In particular the right ventricular outflow tract, the pulmonary artery system, the muscular ventricular septum, and arterial override (five patients) could be more reliably assessed. Major disadvantages of TOE were the limited number of obtainable scan planes, the limited haemodynamic information that could be derived, and the inferior image quality. Exclusion of residual interventricular shunting or residual outflow tract gradients after bypass was impossible with TOE but was reliably performed with EPI. In contrast TOE provided an improved insight into atrioventricular valve function after bypass and permitted continuous monitoring of ventricular function during the immediate and early postoperative period, which was not feasible with EPI.

We conclude that intraoperative TOE and EPI in surgery for congenital heart disease are complementary rather than alternative techniques. The definite advantages of TOE are that it permits continuous monitoring of ventricular function and detailed assessment of atrioventricular valve function; EPI is feasible in every patient, provides almost unlimited scan planes, and allows complete haemodynamic evaluation.

Intraoperative epicardial echocardiography in surgery for subaortic obstruction

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Intraoperative epicardial imaging, colour flow mapping, and pulsed Doppler were used to assess surgical repair in 15 patients with a preoperative precordial echocardiographic diagnosis of subaortic obstruction (14 "discrete" fibromuscular membranes, one tunnel obstruction; age range 2–30 years; mean 11 years). In all patients with surgically proved membranes epicardial imaging correctly identified the septal and lateral insertions of the membrane. Multiple levels of insertion in two patients and the lateral insertions in six patients were shown only by epicardial imaging, as was the precise extent of the tunnel obstruction. These findings modified the surgical approach in three patients. Additional defects were recognised in four patients: (one associated ventricular septal defect, one calcified spur on the aortic valve mimicking a membrane, and two perforated aortic valve cusps). Two wrong echocardiographic diagnoses were made: a reduplicated anterior mitral leaflet was identified as the cause of subaortic obstruction in one patient (diagnosed by epicardial imaging as having a discrete membrane) and reduplicated echoes from a calcified aortic valve leaflet were wrongly interpreted as a calcified membrane in another. Epicardial imaging after bypass showed remnants of the membrane in three patients and confirmed complete enucleation in others. Although colour flow mapping after bypass showed evidence of residual outflow tract turbulence in 13 out of 15 patients, peak systolic velocities by pulsed Doppler after bypass were $<2\cdot5$ m/s in all cases (confirmed on follow up precordial echocardiographic studies). In two patients, mild residual dynamic gradients due to persistent septal hypertrophy were recorded, which disappeared on subsequent follow up. Pre-existing mitral regurgitation (4/15 patients) and aortic regurgitation (11/15 patients) remained unchanged in the postbypass studies.

Epicardial imaging after bypass provides superior morphological information about the precise extent and attachments of subaortic obstructive lesions and of associated defects when compared with precordial echocardiography. Epicardial imaging, pulsed Doppler, and colour flow mapping after bypass permit immediate assessment of surgical repair and the exclusion of significant residual obstruction, mitral regurgitation or aortic regurgitation.

Value of intraoperative epicardial ultrasonography in Fontan type procedures

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We used intraoperative epicardial imaging, colour flow mapping, pulsed and continuous wave Doppler before and after repair in 24 consecutive patients (median age 3 years 9 months) undergoing a Fontan type procedure in order to evaluate any potential value of this technique for surgical decision making and perioperative management. The preoperative diagnosis was tricuspid atresia in 13 patients, double inlet left ventricle in seven patients, and miscellaneous lesions in four. Before bypass epicardial imaging refined the preoperative diagnosis in five (21%) patients, influencing the surgical procedure in three patients (atrioventricular connection *v* direct atriopulmonary anastomosis in two, Glenn shunt *v* atriopulmonary anastomosis in one). After bypass left ventricular diastolic filling and systolic function was monitored in all patients. Colour flow mapping and pulsed wave Doppler allowed the immediate haemodynamic results to be assessed (repair integrity and pulmonary blood flow characteristics). Ventricular augmentation of pulmonary blood flow was documented by pulsed Doppler in two out of three patients with valved homograft atrioventricular connections. After total cavopulmonary anastomosis (five patients) low velocity non-pulsatile flow patterns were observed. Eight important residual lesions were detected in six patients (residual intracardiac shunts in three, mitral valve regurgitation in three, restrictive ventricular septal defect in ventriculoarterial discordance in one, pulmonary artery obstruction in one. From the results after bypass an immediate revision during a second period of bypass was judged to be necessary and feasible in three (12%) patients. One patient with ambiguous results after bypass from colour flow mapping and contrast study (ultrasonic shadowing by prosthetic material) required early reoperation for residual interatrial shunting. Final studies documented optimal repair in 21 (87%) patients. No complications related to the technique were encountered.

Intraoperative Doppler ultrasonography proved to be of unique additional value to the surgical management of patients undergoing a Fontan type procedure. It permitted refinements in the preoperative diagnosis, an excellent assessment of ventricular function, and the identification of residual lesions requiring immediate revision during a second period of bypass.

Verapamil sensitive ventricular tachycardia: effects of vagal manoeuvres and adenosine

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Right ventricular outflow tract (RVOT) tachycardia has been shown to be sensitive to both adenosine and verapamil and is thought to be due to triggered automaticity. Fascicular tachycardia is another form of ventricular tachycardia that is sensitive to verapamil but its mechanism is unknown. We studied the effects of vagotonic manoeuvres, intravenous adenosine (up to 0·25 mg/kg in incremental doses), and intravenous verapamil (0·15 mg/kg) during tachycardia in nine patients (mean age 31 (5) years), two with incessant RVOT tachycardia and seven with inducible fascicular tachycardia. The diagnosis was made at invasive electrophysiological study in all patients. No patient had evidence of structural heart disease. Vagal manoeuvres did not have any effect on any tachycardia. Adenosine interrupted tachycardia in both patients with RVOT tachycardia, for a period proportional to the dose of adenosine (from 25–30 s) but had no effect on tachycardia in any of the seven patients with fascicular tachycardia. Verapamil produced stuttering termination of tachycardia with no change in RR interval in both patients with RVOT tachycardia. In the six patients with fascicular tachycardia who were given intravenous verapamil the arrhythmia was slowed and then terminated (from mean RR interval of 362 (58) ms to 488 (97) ms; $p < 0·01$). In four of these patients RR interval alternation was observed before termination.

The lack of response of fascicular tachycardia to adenosine suggests that the mechanism is different from RVOT tachycardia. The slowing of fascicular tachycardia before termination with verapamil suggests the presence of a calcium channel dependent re-entrant circuit as a basis for the arrhythmia.

Quantitative analysis of the P wave in paroxysmal atrial fibrillation

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Signal averaging of the QRS complex can identify patients at risk of ventricular arrhythmias, yet similar techniques applied to the atria have so far been disappointing. Variability in the underlying disease of the patient groups studied and difficulty in identifying late potentials because of interference by His bundle signals during the PR interval may account for these poor results. Using a template recognition system specific to the P wave, we recorded signal averaged electrocardiograms from nine patients with idiopathic paroxysmal atrial fibrillation and from 15 control subjects. From vector magnitude plots of the P wave we calculated P wave duration, area ratio and root mean square voltage above various frequencies, and peak and mean spatial velocity. Significantly greater high frequency activity and spatial velocity were observed in the group of patients with paroxysmal atrial fibrillation (root mean square) voltage >40 Hz, paroxysmal atrial fibrillation 327 (92) mV, control 235 (34) mV, $p = 0·03$. Peak spatial velocity, paroxysmal atrial fibrillation; 6·44 (1·76) mV/s, control 4·56 (0·16) mV/s, $p = 0·03$).

These observations support previous intracardiac data that implicate delay and fragmentation of intra-atrial conduction in the pathogenesis of paroxysmal atrial fibrillation.

Exaggerated dispersion of repolarisation provoked by premature ventricular stimulation: a mechanism for ventricular arrhythmia

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Exaggerated dispersion of ventricular repolarisation may create a substrate for ventricular arrhythmia. We compared steady state variation in monophasic action potential duration at 90% repolarisation (MAP_{90}) between widely spaced right ventricular endocardial sites (range 7–14, mean 11) at two drive cycle lengths in two groups: group 1 ($n = 10$), patients with normal right ventricular myocardium; group 2 ($n = 10$), patients with disease right ventricular myocardium and ventricular tachycardia (VT). Maximum difference in MAP_{90} at 600 ms drive cycle length in group 1 was 41·5 (7·3) ms, falling to 27·2 (7·8) ms at 430 ms drive cycle length and was not significantly ($p > 0·1$) different from group 2 (31·3 (5·8) ms and 30 (5·5) ms respectively). We next investigated the effect of perturbation of the steady state on difference in MAP_{90} between simultaneously recorded adjacent right ventricular sites in 10 controls and six patients with right ventricular disease and ventricular tachycardia. Ventricular stimuli of increasing prematurity were introduced on a background of continuous pacing at 600 ms drive cycle length, until the effective refractory period was reached. The difference in MAP_{90} between adjacent endocardial sites after premature stimulation at effective refractory period +10 ms was significantly greater ($p < 0·001$) in those with right ventricular disease and ventricular tachycardia (45 (24·5) ms) compared with controls (5 (6·3) ms).

We therefore suggest that dynamic rather than static dispersion of MAP_{90} may contribute to susceptibility to ventricular arrhythmia.

Acceleration of pre-excited tachycardias by adenosine

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The use of intravenous adenosine has been recommended by several groups for the acute management of broad complex tachycardia. The short half life of this agent, however, has precluded assessment of its effects on refractoriness of accessory pathways and its effects on pre-excited tachycardias are not known. To assess the effects of adenosine in this condition it was administered to 26 patients with pre-excitation. Intravenous adenosine (12 mg) was administered to seven patients (group 1) during atrial pacing at a cycle length 20 ms below that required to cause stable 2:1 conduction block in the accessory pathway (mean pacing cycle length 266 (35) ms). After adenosine transient 1:1 conduction occurred through the accessory pathway in six of the seven patients, indicating a shortening of anterograde refractoriness. In two patients this effect was abolished after intravenous propranolol (10 mg). Adenosine was given to 19 patients (group 2) during induced pre-excited tachycardia at a mean dose of 0·16 mg/kg (range 0·1–0·25). Pre-excited atrial flutter was accelerated in four patients owing to shortening of flutter cycle length (203 (5) ms to 163 (13) ms; $p < 0.05$). The minimum RR interval in pre-excited atrial fibrillation decreased in seven out of eight patients (259 (50) ms to 230 (42) ms; $p < 0.01$). Pre-excited junctional tachycardia was terminated in five out of seven patients. In one patient antidromic tachycardia accelerated (cycle length 340 ms to 250 ms) owing to a sudden shortening of ventriculoatrial conduction time with no detectable change in atrial activation sequence.

Intravenous adenosine causes a decrease in the anterograde refractoriness of accessory pathways and a decrease in minimum RR interval during pre-excited atrial fibrillation. Adenosine may also cause an increase in the ventricular rate of pre-excited atrial flutter and antidromic tachycardia through mechanisms independent of accessory pathway anterograde refractoriness.

High fidelity right atrial pressure recording during cardiac arrhythmias

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The performance of a high resolution (33 Hz) fibreoptic pressure catheter within the right atrium was studied during cardiac arrhythmias. In 15 patients (mean age 35 years, nine females) undergoing electrophysiological study the unfiltered signal was amplified and recorded on to paper. During sinus rhythm and atrial pacing a constant amplitude deflection occurred during atrial systole (a wave). During atrioventricular re-entrant nodal (six patients) the a wave was simultaneous with ventricular systole (v wave), producing a characteristic sinusoidal pattern. In atrioventricular re-entrant tachycardia (four patients) the a wave produced a characteristic distortion of the sinusoidal pattern. In atrial fibrillation (three patients) the waveform was of varying amplitude and frequency, and during atrial flutter a waves occurred alternately with v waves. During ventricular tachycardia without ventriculoatrial conduction (two patients) there were large amplitude, irregular deflections unrelated to the ventricular electrogram.

High fidelity pressure recordings produced characteristic appearances for pattern recognition of each arrhythmia studied. It permitted determination of the temporal relation between electrical and mechanical cardiac events and may have potential in the detection and recognition of cardiac arrhythmias.

Recurrence of accessory pathways after surgery: septal pathways and the "rim effect"

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Surgery for atrioventricular accessory pathways was performed on 87 patients (53 male, mean age 31 years, range 11 to 68 years) with 91 pathways. Seventy-six patients had ventricular pre-excitation; 44 pathways were left free wall, 20 left posteroseptal, eight right posteroseptal, six right free wall, and 13 anteroseptal. Four patients had two pathways (three left free wall and left posteroseptal, one left free wall and anteroseptal). Endocardial dissection was performed in 74 patients, supplemented with cryoablation in a further four patients, seven patients had epicardial dissections plus cryoablation, and two patients had a combined approach. The pathways recurred in eight patients (9%), three within one week of operation and five more than one month from operation. Seven of the recurrences were in the first 50 patients. No recurrences were due to a second pathway. Twenty percent of left posteroseptal pathways and 31% of anteroseptal pathways recurred, while only 4% of free wall pathways recurred. Reoperation was successful in all patients. Two patients with recurrence of their left free wall pathways had pre-excitation of the same electrocardiographic morphology as preoperatively, but with a longer P delta interval. At reoperation the earliest atrial activation during tachycardia had changed to the left posteroseptal position. Cryoablation or incision into the mitral annulus in this position resulted in abolition of the pathways in both patients. The same phenomenon was subsequently observed intraoperatively in two further patients, and again cryoablation or incision into the mitral annulus in this area abolished the pathways. This phenomenon can be explained by the atrial insertion of the pathway being in a rim of atrial tissue left on the mitral annulus after dissection. Thus, retrograde activation of the atria is through the exit of the rim in the posteroseptal region, whereas anterograde conduction is unchanged but prolonged.

We conclude that left posteroseptal and anteroseptal pathways have a higher recurrence rate than free wall pathways (6/33 *v* 2/58; $p < 0.05$), and this should influence selection of patients for surgery. Repeat surgery is successful in abolishing these pathways. Care must be taken with left free wall pathways to prevent conduction through an atrial rim.

Cerebral metabolic autoregulation is disturbed in children undergoing cardiopulmonary bypass

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There is a high incidence of neurological morbidity after paediatric cardiopulmonary bypass surgery. Our hypothesis is that cardiopulmonary bypass surgery disturbs the autoregulation of cerebral blood flow in relation to cerebral metabolic rate, making children susceptible to ischaemic brain damage at times of low cerebral perfusion or high cerebral metabolic rate. We made 73 serial measurements of cerebral blood flow and cerebral metabolism in 17 children (aged 6 weeks–6 years) undergoing cardiopulmonary bypass surgery. A standard anaesthetic was used (enflurane 0·2%, fentanyl 30 µg/kg, membrane oxygenator). Cerebral blood flow was measured with the Kety Schmidt technique and cerebral consumption or production of oxygen, lactate, and pyruvate determined by arteriosuperior jugular venous bulb concentration differences (AJVD) × cerebral blood flow. Cerebral blood flow ranged from 0·09–1·38 ml/g/minute and cerebral oxygen consumption from 125–4658 nmol/g/minute. Metabolic autoregulation of cerebral blood flow was disturbed in all children. Before and after cardiopulmonary bypass, high cerebral metabolic rates (up to three times normal) were associated with normal cerebral blood flow. That cerebral blood flow was insufficient for cerebral metabolic rate was indicated by AJVDO$_2$s up to four times normal and significant cerebral lactate production. The closest link between cerebral blood flow and cerebral metabolic rate occurred during hypothermic bypass when metabolic rates and blood flows were both lower than normal and AJVDO$_2$s were close to the normal range.

We conclude that children undergoing cardiopulmonary bypass have disturbed metabolic autoregulation, the effects of which are minimised during hypothermia. That this occurred before bypass suggests that the stress response to major surgery—for example, sternotomy—may have adverse effects on cerebral autoregulation.

Pulmonary autograft for aortic valve replacement: 22 years later

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Not presented

Preserved endothelial dependent response to intracoronary substance P in cardiac transplant recipients

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The endothelium dependent vasodilator substance P dilates normal and diseased coronary vessels in humans in vivo and produces a maximal response similar to that seen with intracoronary isosorbide dinitrate (ISDN). Twelve cardiac transplant recipients underwent intracoronary infusions of substance P after their annual investigations. All patients were well with no evidence of rejection and with angiographically normal coronary arteries and no evidence of accelerated coronary sclerosis. Substance P in increasing doses was infused at 2 ml/min for two minutes into the left coronary circulation in 11 transplant recipients and into the right coronary artery in one recipient followed by 2 mg isosorbide dinitrate infused over two minutes. Coronary artery diameters were measured in 23 vessel segments in 12 transplant recipients. The following doses of substance P (pmol/l) were infused: saline, 1·4, 2·8, 5·6, 11·2, 22·4, and isosorbide dinitrate. The mean (SE) percentage increase in diameter to increasing doses of substance P were as follows: 0 (0), 6·5 (2·9), 10·9 (2·9), 12·1 (2·9), 16·5 (2·6), 19·2 (3·1), 25·8 (2·2) respectively. In 15 vessel segments the maximal response occurred at the two maximal doses of substance P and the remainder produced the maximal response at the lower doses of 2·8 and 5·6 pmol/l. The maximal response to substance P was 22% (SE 2·5%) (mean percentage change in diameter). This was not significantly different from that achieved with isosorbide dinitrate. There was preserved endothelial dependent vasodilation in transplanted coronary arteries to substance P comparable with that seen with nitrates.

We conclude that coronary endothelial function is preserved in transplant recipients and that substance P provides a useful tool for testing endothelial function in these patients.

Adenosine enhances the efficacy of hypothermic cardioplegic arrest

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We previously showed the beneficial effect of adenosine during reperfusion after ischaemic arrest. This study was designed to evaluate its potential role as an additive during hypothermic cardioplegia in a dose-response study in the isolated working rat heart. With a protocol that mimics clinical practice in the United Kingdom groups of hearts were subjected to three hours of ischaemic arrest at 20°C with multidose infusions of St Thomas's Hospital cardioplegic solution No 1 every 30 minutes. Adenosine was added to the cardioplegic solution in concentrations of 0 (control), 0·1, 5·0, 10·0, and 20·0 mmol/l. Six hearts were studied in each group. The recovery of cardiac function was enhanced in all hearts that received adenosine, and the optimum concentration was found to be 10 mmol/l. Mean recovery of cardiac output (expressed as a percentage of its preischaemic control value) in this group was 61·8% (3·7%) in contrast with 35·4% (5·1%) in the control group ($p < 0·01$). Thus, in its optimal concentration, adenosine improved the efficacy of the cardioplegic solution by almost 75%. Parallel metabolic studies were performed to determine myocardial nucleotide content at various times. Adenosine significantly increased coronary flow during the ischaemic period, and its beneficial effect might have been mediated by better perfusion of the microvasculature.

These observations further support the suggestion that adenosine may have potential in surgical practice, particularly during extended periods of cardioplegic arrest.

Does hyperglycaemia contribute to intellectual dysfunction after cardiac surgery?

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Evidence from published work on animals and clinical evidence from published work on stroke and cardiac arrest suggests that hyperglycaemia during cerebral ischaemia can influence cerebral recovery after an ischaemic insult. If the cerebral changes that occur after cardiopulmonary bypass are caused by microemboli and are therefore ischaemic in origin then hyperglycaemia during cardiopulmonary bypass may be important.

Routine practice at this hospital has been to use either a 5% dextrose or Hartmann's solution prime in the cardiopulmonary bypass circuit. There was no gross clinical difference between the two sets of patients. It was therefore considered ethically acceptable to study the outcome in the two groups in a prospective study. Seventy patients having elective coronary revascularisation were prospectively randomised into either of the primes. The groups were comparable in age, sex, and bypass and cross clamp times. Neuropsychological assessment was performed with a well proved test battery before and eight weeks after surgery. Blood glucose concentrations rose to a mean of 26 mmol/l in the 5% dextrose group and 6 mmol/l in the Hartmann's group during bypass. There were no deaths in either group, there were two clinical neurological events, both occurring in the hyperglycaemic group, and both patients made good recoveries. Neuropsychological deficit was defined as a deterioration in two or more tests of 1 SD from the preoperative mean group score between preoperative and eight week testing. With this definition there was no difference between the groups; 38% of patients in each group showed significant deficits. More detailed analysis of the results did, however, show differences. When score changes between the pre-operative and eight week tests were assessed it was found that in 17 out of the 18 versions of the tests more patients in the hyperglycaemic group deteriorated than did the normoglycaemic controls. With a two tailed binomial statistic this difference was significant.

Hyperglycaemia may be a detrimental factor in the development of intellectual morbidity after cardiac surgery. We advocate the use of a non-glucose containing prime, regular monitoring of plasma glucose concentration, and the prompt correction of hyperglycaemia should it occur during cardiopulmonary bypass.

Mechanical support for acute ventricular failure

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In 1989 a total of nine adults had short to medium term ventricular assistance with the Centrimed centrifugal pump. The eight male patients and one female patient (age range 21 to 54 years) all had severe ventricular failure that could not be managed without full support for one to five days. Six patients had left ventricular assistance, one had bilateral support, and the remaining two patients had right sided support only. Complications included severe bleeding necessitating further exploration and renal failure; there were no problems from emboli or from failure of the centrifugal pump itself. Of the four survivors, two had peritransplantation acute heart failure, one was used as a deliberate bridge to cardiac transplantation after arrythmia surgery, and the fourth was weaned from his device after five days of support. The survivors all had their device inserted at an early phase in their decline, illustrating the importance of patient selection and timing. All survivors were New York Heart Association class I, including the one weaned patient, whose ventricle was barely contracting at the time of insertion.

The cost of the centrifugal pumps is cheap relative to the cost of sophisticated ventricular assist devices and provides encouraging results for medium term support. The use of these pumps in the context of acute cardiogenic shock may prove worth while.

Potential impact of population screening for prenatal diagnosis of congenital heart disease

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Mid-trimester screening for detection of congenital heart disease (CHD) is now advocated in the United Kingdom. To assess the potential impact we reviewed 350 consecutive neonatal admissions up to September 1989 (group A), and prospectively assessed 81 consecutive infants admitted since then (group B) at a single centre. Severe CHD was defined as lesions requiring high risk, multiple, or purely palliative surgery for survival. In group A 167 and of 350 (47%) patients, all with severe CHD, could have been detected on a screening four chamber view at 18–20 weeks' gestation. In group B 55 out of 81 (68%) patients, all with severe CHD, were potentially detectable prenatally; 16 out of 26 of the remainder also had severe CHD. Only 1 out of 81 (1%) did not have CHD. All 81 had received fetal ultrasonography, but scanning was performed only before 18 weeks' gestation in 54 out of 81 (67%), too early to reliably detect CHD. Six out of 81 (7%) were high risk pregnancies for CHD, and 6 out of 81 (7%) had extracardiac anomalies. Third trimester diagnosis of severe CHD occurred in five cases. Reassurance to mothers that the fetal heart was normal had been provided in 37 out of 81 (46%). Forty one out of 71 (58%) mothers in group B with infants with severe CHD volunteered their preference for termination of pregnancy if mid-trimester diagnosis had been available.

Consequently, midtrimester detection of CHD rarely occurs despite almost universal fetal scanning. Major training at primary scan level and modifications of the timing of existing fetal anomaly scanning is required, but the potential impact of effective screening on the incidence of severe CHD postnatally is considerable.

Use of flecainide in fetal atrial tachycardia

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Flecainide is a potent antiarrhythmic drug that has been shown to be valuable in treating atrial, junctional, and ventricular arrhythmias. After recent reports of the adverse side effects of flecainide treatment, however, it has been advised that this drug should be confined to high risk patients and those with life threatening arrhythmias. The intrauterine development of a fetal tachycardia and heart failure is a life threatening condition for the fetus with a mortality that is reported to be between 20% and 50%. Many drugs have been reported to be useful in the treatment of fetal tachycardias—for example, digoxin, verapamil, quinidine, procainamide, amiodarone, and propranolol—giving some indication of the difficulty of managing these cases successfully. We used flecainide in a group of 13 patients for a fetal atrial tachycardia associated with intrauterine cardiac failure. Eleven of the 13 patients responded by conversion to sinus rhythm. One fetus died in utero and one fetus the rhythm subsequently converted with alternative treatment. Of the 11 patients, nine were alive and well three months to two years after delivery and two are not yet delivered. These results compare favourably with previous forms of antiarrhythmic treatment used in the fetus.

Flecainide is a useful drug in selected cases of fetal atrial tachycardia associated with intrauterine cardiac failure, but its use should be restricted to centres experienced in the management of these cases.

R wave synchronised atrial pacing as an adjunct to the management of His bundle tachycardia after surgery

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Eleven children aged 3 days to 13 years were treated with R wave syndronised atrial pacing for His bundle tachycardia (HBT) after bypass cardiac surgery for various cardiac anomalies. All patients developed severe low cardiac output with the onset of HBT. Maximum rate of HBT was 170–250 beats/min. Eight children were treated with antiarrhythmic drugs, including amiodarone in six, flecainide in one, and digoxin in three, with some decrease in rate. Ten children were surface cooled to a core temperature of 32°C or less, which similarly resulted in a decrease in rate without restoration of sinus rhythm. Atrial pacing restored atrioventricular synchrony in each patient. The pacing stimulus was synchronised either manually or automatically to the R wave of the HBT so that atrial depolarisation preceded the next R wave by an appropriate PR interval. The blood pressure increased immediately with the onset of atrial pacing in 10 (mean 15 mm Hg). This was associated with an increase in urine output and allowed a decrease in inotropic support. One child developed atrial flutter necessitating cardioversion but no other side effects were seen. Despite these measures four children died. Of the 7 survivors, six sustained sinus rhythm which developed from 2 to 10 days after the onset of HBT. One child has severe neurological impairment as a consequence of low cardiac output, the others are alive and well.

The R wave synchronised atrial pacing is a useful adjunct to the management of life threatening HBT after surgery.

Effect of balloon dilatation of right ventricular outflow tract on size of pulmonary valve annulus and arteries in tetralogy of Fallot

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The effect of balloon dilatation of right ventricular outflow tract on the pulmonary valve annulus and arteries was evaluated in six children with tetralogy of Fallot who required palliation for increasing cyanosis. A total of 13 procedures were performed. The age at the first balloon dilatation ranged from 0·6 to 12·7 months (mean 7·2 months). The diameters of the pulmonary valve annulus and right and left pulmonary arteries were measured angiographically before the balloon dilatation and a mean of 4·8 months (range 1·5–9·6 months) later at the next procedure. Pulmonary valve annulus diameter increased from 7·1 (2·2) mm before to 9·8 (2·4) mm after balloon dilatation ($p = 0{\cdot}01$); diameter of the pulmonary arteries increased from 6·9 (1·9) mm to 8·9 (1·7) mm on the right ($p < 0{\cdot}01$) and 6·7 (2·6) mm to 8·0 (2·6) mm on the left ($p < 0{\cdot}01$). Predicted right ventricular to left ventricular systolic pressure ratio after surgical correction without a transannular patch based on these measurements decreased from 0·8 (0·22) before to 0·58 (0·10) after balloon dilatation. No surgical shunts were required for palliation. Three of the patients had surgical correction at a mean age of 18 months.

In conclusion, these results show that there is an increase in size of the pulmonary valve annulus and pulmonary arteries after balloon dilatation in tetralogy of Fallot.

Continuous wave Doppler after surgical repair of coarctation of the aorta

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High flow velocities in the descending aorta may sometimes be detected by continuous wave Doppler after satisfactory repair of coarctation. To investigate this phenomenon the pressure gradient across the aortic arch and flow velocities in the descending aorta were measured simultaneously in 20 patients aged 4·7 to 33 years undergoing cardiac catheterisation. Peak to peak and instantaneous peak pressure drop across the arch were measured with a double lumen catheter. Velocity in the descending aorta was recorded with a continuous wave transducer from the suprasternal notch and peak pressure drop was calculated with the modified Bernoulli equation. Catheter instantaneous peak gradient was higher than peak to peak in all but one case with variable differences (−2 to +31 (mean 12·4) mm Hg) between the two measurements. Similarly, Doppler instantaneous peak gradient was higher than catheter peak to peak with differences of −3 to +28 (mean 11·5) mm Hg. Comparison of Doppler and catheter instantaneous peak gradient showed a mean difference of only 0·9 mm Hg, but individual differences ranged from −17 mm Hg to +22 mm Hg. These errors may be due to poor alignment with flow, inability to measure and correct for proximal flow velocity with continuous wave Doppler, and complex flow dynamics in the aortic arch.

Continuous wave Doppler gradient after repair of coarctation must be interpreted with caution. It is almost always higher than peak to peak pressure drop at catheter and even when compared to instantaneous peak gradient, measured invasively it may importantly overestimate or underestimate pressure drop.

Primary balloon coarctation aortoplasty in neonates

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Primary balloon coarctation aortoplasty was attempted in 10 consecutive neonates (age range 2–23 days) with coarctation of the aorta. Associated abnormalities included transposition of great arteries (one), ventricular septal defect (five) and ductus artenosus (five, including three receiving alprostadil). It was not possible to cross the coarctation site in one patient. In two patients with severe isthmal hypoplasia there was no change in the gradient after dilatation. In the remainder the residual gradients were trivial (gradient before dilatation, 33 (13), after 7 (8) mm Hg, $p < 0{\cdot}001$) and angiography showed complete relief of coarctation. Two patients subsequently had no evidence of recoarctation 22 and 37 weeks after dilatation. Five developed severe recoarctation between 5 and 12 weeks after dilatation. Recoarctation was rapidly progressive in three, there having been no appreciable gradient on Doppler as recently as two weeks before its development, and more slowly progressive in two. Three patients underwent a second dilatation procedure. One patient subsequently remained well with no residual gradient 18 weeks later. Restenosis occurred within eight weeks in the other two. All failures have undergone successful surgical repair.

Primary balloon aortoplasty can be performed in most neonates with excellent immediate results. Severe isthmal hypoplasia is, however, a contraindication to balloon dilatation and early restenosis is an important problem. These results do not support the continued use of primary balloon coarctation aortoplasty in neonates.

Standardised exponential exercise protocol

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The development of a standardised exercise protocol has been hindered by the use of different exercise modes. On a treadmill work at each stage is dependent on body weight, but during bicycle exercise work is weight independent. We have designed a new treadmill protocol with one minute stages, beginning at a low workload (predicted oxygen consumption ($\dot{V}O_2$) 7 ml/kg/min) and increasing exponentially to a predicted $\dot{V}O_2$ of 50 ml/kg/min after 15 minutes (standardised exponential exercise protocol (STEEP) test). After adjustment for body weight this protocol is also suitable for a bicycle ergometer. The STEEP test was initially validated in 30 normal male subjects (aged 29–55), each of whom performed the two protocols in random order. The mean $\dot{V}O_2$ rose exponentially, and close agreement was observed between the treadmill and the bicycle protocols. A higher proportion of subjects completed the treadmill protocol (27 *v* 15; $p < 0{\cdot}005$). Submaximal heart rates were slightly higher during the bicycle test. Twenty subjects with mild to moderate heart failure ($\dot{V}O_{2max}$ 12–25) were then exercised to symptom limited maximum with the STEEP tests. The mean $\dot{V}O_2$ was similar for each stage of the treadmill and the bicycle protocols, as in the normal subjects. Exercise time and $\dot{V}O_{2max}$ were, however, significantly higher with the treadmill test.

This protocol is the first to use an exponential rise in workload. By adjusting for body weight similar mean $\dot{V}O_2$ was obtained for each stage of the bicycle protocol as the treadmill protocol in both normal subjects and patients with heart failure. As $\dot{V}O_{2max}$ is higher with treadmill testing, however, the exercise time is also significantly longer.

Role of intraoperative epicardial ultrasonography in surgery for congenital heart disease

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In a prospective study we used intraoperative epicardial echocardiography (cross sectional imaging (epi-2D)), colour flow mapping (CFM), and pulsed and continuous wave Doppler (PW, CW) in 308 patients both before and after cardiopulmonary bypass for total correction of congenital heart disease to determine the potential value of this technique in surgical management. Lesions studied were isolated ventricular septal defect (76), atrial septal defect (eight), atrioventricular septal defect (31), Ebstein's malformation (nine), Fontan procedures (24), transposition of great arteries (45), Fallot (19), double outlet right ventricle (11), left ventricular outflow tract obstruction (15), aortic or mitral disease (16), miscellaneous (36), and reoperations (18). Studies before repair (epi-2D, CFM, PW) refined the pre-operative diagnosis in 87 (28%) patients; this influenced surgical management in 36 (12%) and altered the preoperative diagnosis in 10 (3%). Studies before bypass were, however, incomplete (11 patients) or misleading (seven patients) in 6% of the patients.

Studies after repair permitted the immediate assessment of the surgical repair, and the monitoring of volaemia and ventricular function and aimed at excluding any significant residual lesion. Based on the results of these studies immediate revision during a second period of bypass was performed in 10 (3·3%) patients. The haemodynamic information obtained was valuable for postoperative management in about a quarter of the patients. Only two patients required early reoperation (one because of missed lesions, one because of misinterpretation). Problems inherent in the interpretation of the epicardial studies were (*a*) flow masking behind prosthetic material used for the repair; (*b*) limited access (large transducers relative to sternotomy); (*c*) multiple transducers being required for complete investigations; and (*d*) difficulty in measuring residual lesions. On line interpretation is a problem. Relevant complications were not encountered.

The major contributions of intraoperative Doppler ultrasonography to surgery for congenital heart disease are that it can yield new or more detailed morphological information before repair, it is remarkably accurate in the identification of significant residual lesions, and it is valuable in the complex interactions of volume state and ventricular function after bypass.

Ambulatory haemodynamic monitoring: a new method for simultaneous recording of pulmonary and systemic arterial pressures and ST segment

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A modified (digital) Oxford system for recording intra-arterial blood pressure and frequency modulated electrocardiogram has been combined with a new method for long term pulmonary artery pressure monitoring. A catheter tip manometer is inserted into the pulmonary artery in a specially profiled sheath which allows isolation of the sensor for in vivo gain and zero drift calibration. All signals are recorded on to a modified MR10 recorder, pressure waveforms being in digital format, sampled at 40 Hz with 0·3 mm Hg resolution. The frequency response of the sheath or sensor was flat from 1 to 20 Hz with negligible phase distortion or square wave overshoot. The recording reply system has a band width of 20 Hz and was linear within 0·6 mm Hg from 0 to 70 mm Hg. Beat by beat pulmonary artery pressures obtained by this system simultaneously with an on line statham P50 transducer showed preserved waveforms and pressures within 0·3 mm Hg (systolic) and 2·0 mm Hg (diastolic) during pacing tests. Recordings in 24 subjects over 24–58 hours gave a pulmonary artery pressure range of 17/2–57/34 mm Hg. Each recording had 5–10 calibrations showing start end zero drift of −2 to +2 mm Hg, with some intermediate calibrations giving −3·5 to +7·5 mm Hg drift; in the latter case the transducer failed. Reproducibility between days 1 and 2 of the recording (n = 20) was 1·8/0·9 mm Hg.

This system provides accurate long term pressure recordings combined with ST segment analysis for the study of myocardial ischaemia and function and for the assessment of interventions.

Angiographic and ischaemic correlates of transient dilatation of the left ventricle on dipyridamole stress thallium-201 testing

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The occurrence and significance of transient ischaemic dilatation of the left ventricle (TID) during dipyridamole thallium-201 scintigraphy was studied in 73 patients undergoing coronary angiography. The TID ratio was calculated by dividing the computer derived left ventricular area on the initial anterior planar image by the image at four hours. The extent of ischaemia was assessed by using the Thallium 201 reversibility score (initial—four hour score) and a score of > 7 used to represent extensive ischaemia. In 11 patients with non-significant (< 50%) stenosis the TID ratio was 0·98 (0·046). An abnormal TID (> 3 SD) was defined as ≥ 1·12. The 15 patients with abnormal TID had a higher incidence of critical (≥ 90%) stenosis (93%), collaterals (67%), and extensive ischaemia (54%) and a lower incidence of myocardial infarction (33%) than the 58 patients with a normal ratio (55%, 24%, 12·5%, and 72% respectively; p < 0·05). The incidence of dipyridamole induced positive electrocardiograms, increased lung uptake and chest pain was not significantly different. An abnormal TID ratio was a sensitive (63%) and specific (85%) marker of triple vessel critical coronary disease.

Thus, TID may be observed during dipyridamole thallium-201 testing and implies extensive myocardial ischaemia caused by underlying critical coronary stenosis.

Adverse respiratory reactions to intravenous dipyridamole for myocardial stress thallium studies

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To assess whether the use of dipyridamole stress in myocardial thallium studies is associated with adverse respiratory effects 22 consecutive adults (12 subjects with chronic reversible airflow obstruction and 10 with no history or signs of respiratory disease) referred for imaging were studied with serial spirometry before and during the stress imaging procedure. Triplicate measures of forced expiratory volume in one second (FEV_1) were taken at baseline, at subsequent spirometry repeated 10 minutes after starting dipyridamole infusion (0·57 mg/kg), and again at 25 minutes after initial cardiac imaging. Analysis of variance was used to assess the effect of the drug on respiratory function. Individual responses were varied, but overall there was a significant decline in FEV_1 from baseline, with a mean (SE) reduction of 42 (9) ml (p < 0·0001) at 10 minutes and of 48 (9) ml (p < 0·0001) at 25 minutes; in most cases the change was asymptomatic. In those with chronic reversible airflow obstruction resting FEV_1 fell by 4·5% (58 (11) ml; p < 0·0001) at 10 minutes, and by 4·7% (61 (11) ml; p < 0·0001) at 25 minutes compared with falls of 1·0% (22 (15) ml; NS) and 1·4% (33 (15) ml; p < 0·05) at 10 and 25 minutes in those without respiratory disease. In two subjects, both with chronic reversible airflow obstruction, symptomatic worsening breathlessness developed associated with falls in FEV_1 of 12% (196 ml) and 23% (123 ml) respectively. In one, breathlessness and change in FEV_1 abated spontaneously by 35 minutes. The other subject and another subject with a fall of 11% (160 ml) without breathlessness were given intravenous aminophylline with prompt alleviation of symptoms and changes in FEV_1. In none did examination or lung uptake support a diagnosis of pulmonary congestion. Changes in FEV_1 were unrelated to presence or absence of reversible myocardial thallium defect.

The use of intravenous dipyridamole for cardiac studies can cause reduction in FEV_1 sufficient to be clinically important for those subjects with known chronic reversible airflow obstruction and can induce clinical asthma. Aminophylline seems rapidly to reverse these effects and should be available for immediate intravenous use should this occur.

Role of transoesophageal echocardiography in evaluation of atrial baffle function

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Abnormalities of atrial baffle function can develop early or late postoperatively after an atrial correction procedure and may occur in patients with and without symptoms. Methods previously used to assess atrial baffle function have included precordial echocardiography and cardiac catheterisation. Single plane transoesophageal echocardiography (TOE) can provide an optimal assessment of the atrial morphology and flow patterns within both atrial chambers. To evaluate whether TOE offers an alternative investigative approach to the spectrum of atrial baffle abnormalities we investigated 15 patients (14 Mustard, one Senning; mean age 16·3 years) on an outpatient basis (eight adults) or under heavy sedation or during general anaesthesia for cardiac catheterisation (seven children). TOE findings were compared with those derived from precordial echocardiography and cardiac catheterisation in every case. Furthermore, the transoesophageal scan planes that must be recorded for evaluation of the whole systemic and pulmonary venous pathways were correlated with anatomical specimens. As precordial ultrasonography permitted the visualisation only of the supramitral portion of the systemic venous pathway it failed to identify the wide range of systemic venous baffle abnormalities present (3/15). TOE studies using cross sectional imaging, colour flow mapping, and pulsed Doppler showed superior limb obstruction in six patients (three severe, three mild), mid-baffle obstruction in two, and inferior limb obstruction in two. The entire pulmonary venous pathway could be scanned by both TOE and precordial echo cardiography. Both techniques identified three cases of mid-pulmonary venous obstruction (two mild, one moderate). Individual pulmonary vein velocity profiles however, could be recorded only with TOE pulsed Doppler. Precordial studies detected residual baffle leaks (one large, two small), in only three patients whereas TOE flow mapping identified 11 such baffle leaks (one large, 10 small), which in two patients were multiple.

We conclude from these findings that TOE was of great additional value in the definition of a range of often clinically unsuspected baffle abnormalities. In our opinion it is likely to become the investigative method of choice for baffle malfunction.

Residual ductal tissue in aorta: histological study in resected specimens of coarctation

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Subclavian flap aortoplasty for coarctation repair in the first three months of life has been associated with a significant incidence of recurrence. Having had such an experience, we extended the use of resection and end to end anastomosis to this age group. The histological findings in 23 specimens resected between 1985 and 1987 are reported and the implications for recurrent coarctation are discussed. In 22 of the 23 specimens there was a circumferential sling of ductal tissue around the aorta at its junction with the ductus. In all 22 cases projections of ductal tissue extended distally for a variable length from the sling. These projections were on the side of the aorta opposite the ductus and on the aorta below its junction with the ductus. The most distal part of the projections were not completely excised in 11 patients. The aortic incision in subclavian flap aortoplasty is likely to be within the projection of ductal tissue opposite the ductus and may or may not extend beyond it into normal aortic tissue. There would then be a residual oblique circumferential sling of ductal tissue passing beyond the apex of the flap, the maturation of which could lead to recurrence coarctation.

In conclusion, these findings suggest a histopathological basis for recurrence of coarctation after subclavian flap aortoplasty and support the view that the flap should extend far down the descending aorta.

Magnetic resonance imaging: evaluation of the pulmonary arteries in right heart obstruction

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Since November 1987 the pulmonary arteries of 30 patients (age range 0·03 to 12·8 years, mean 3·0 years) with obstruction of the outflow of the right ventricle have been studied with a 1·5 T magnetic resonance imaging system. Fifteen had tetralogy of Fallot, two double outlet right ventricle with pulmonary stenosis, and 13 pulmonary atresia. Nineteen of the studies used a head coil (32 cm) and the remainder in the older age group used the standard body coil. All 30 children had echcardiography before magnetic resonance imaging and 27 had angiography. Multiple slices (5–7 mm thick) were acquired in straight or oblique transverse and coronal planes, depending on individual anatomy. The images obtained were subsequently reviewed to evaluate our ability to show pulmonary artery anatomy. In two patients presence of central pulmonary arteries was excluded. In 27 of the patients the pulmonary trunk, the bifurcation, and right pulmonary artery up to the first hilar branch were well demonstrated. The left pulmonary artery was more difficult to image successfully. It was imaged in its entirety in 12, these patients being predominantly in the most recent part of the series. Only the proximal portion was imaged in another 13 patients. In three patients the imaging of the left pulmonary artery was unsuccessful. The best images of the left pulmonary artery were obtained in various planes in different patients. The most consistently successful plane was oblique coronal planned from the initial transverse images.

Magnetic resonance imaging of the pulmonary arteries in patients with congenital heart disease is a valuable additional technique, but successful imaging requires careful selection of appropriate oblique imaging planes.

Comparative roles of epicardial and precordial echocardiography in the assessment of surgical repair for congenital heart defects

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In 94 consecutive patients (age range 3 days–68 years; mean 7 years) undergoing surgical repair of a congenital heart defect via a median sternotomy the results of epicardial cross sectional (epi-2DE) and Doppler colour flow imaging after bypass were compared with those of sequential precordial echocardiography (*a*) within 24 hours of surgery and (*b*) after hospital discharge. There were two intraoperative deaths and two early deaths (within 10 days of surgery) associated with poor systemic ventricular function on epi-2DE. In the remainder during subsequent precardial echocardiography the systolic blood pressure was greater than at epi-2DE by a mean of 24 mm Hg (range -15 to $+40$ mm Hg). In six out of seven patients with significant residual defects, epi-2DE and Doppler colour flow imaging correctly identified the defect, enabling surgical revision during a second period of bypass. In one patient a residual shunt at atrial level after a total cavopulmonary anastomosis was identified by contrast precordial echocardiography 24 hours later and required immediate reoperation. Minor degrees of peripatch shunting was a common finding, and persisted at the time of hospital discharge in 17 out of 46 patients who had undergone patch closure of a ventricular septal defect as part of the surgical procedure. Additional trabecular ventricular septal defects were missed on epicardial colour flow imaging in three patients, one of whom required subsequent reoperation. Epi-2DE with spectral Doppler underestimated residual outflow tract gradients in five patients who had calculated instantaneous systolic gradients on follow up precardial echocardiography of between 50 and 70 mm Hg. Residual left atrioventricular valve regurgitation after repair of complete atrioventricular septal defect was also underestimated by epicardial colour flow imaging in three patients.

Epi-2DE and Doppler colour flow imaging permits the recognition of the majority of residual defects requiring immediate reoperation. Documentation of poor ventricular function after bypass was associated with a higher mortality. Assessment of residual outflow tract gradients or valve regurgitation by epicardial echocardiography is, however, inaccurate in view of the rapidly changing haemodynamics.

Intraoperative ultrasound assessment of the arterial switch operation

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The arterial switch operation induces acute changes in both ventricular function and geometry. The time course and nature of these changes immediately after bypass and their relation to the final outcome has not previously been documented. Final outcome is also determined by other factors such as successful coronary reimplantation and unobstructed great vessel anastomosis. Intraoperative ultrasound studies might be able to monitor the changes in both global and segmental left ventricular function and define any significant residual anatomic lesion. Therefore 37 consecutive patients (31 neonates) undergoing a switch operation were studied prospectively by epicardial ultrasonography using cross sectional and M mode echo cardiography, colour flow mapping, and spectral Doppler. Echocardiography before bypass documented the relative size and function of the left and right ventricles and septal geometry and motion. Ventricular septal defect morphology was confirmed in 13 patients. Unsuspected morphological findings were documented in four patients (11%). Adequate visualisation of coronary morphology was difficult and two out of three intramural coronaries were missed. Studies after bypass showed that the increase in left ventricular size and changes in the geometry of both ventricles were immediate. There was wide variation in early left ventricular function as assessed by M mode echocardiography and computer assisted cross sectional wall motion analysis, which did not relate to final outcome (no deaths intraoperatively and only one postoperatively). On line left ventricular function assessment was valuable in optimising volume loading and inotropic treatment. Septal dyskinesia was a common finding. Discrete segmental dyskinesia of the posterior left ventricular wall was seen in one patient, leading to the diagnosis of a circumflex artery compression; immediate surgical revision (Lecompte manoeuvre) resulted in rapid normalisation of posterior wall motion. Further residual lesions documented but not required surgical revision included mild neoaortic (two patients) or neopulmonary (five patients) incompetence and three tiny ventricular septal defects. Immediate aortic or pulmonary anastomotic gradients were excluded in all.

We have confirmed that intraoperative ultrasonography provides unique information on the acute changes in left ventricular geometry and function after a switch procedure, and that it is a sensitive method for the exclusion or diagnosis of any significant residual morphological lesion.

Ventricular septal defect in Yucatan miniature pigs

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In an effort to associate morphological features of ventricular septal defect with patterns of inheritance we studied the hearts from a colony of Yucatan miniature pigs with spontaneously occurring congenital heart defects. Ventricular septal defect was encountered in 57 out of 81 neonates from 15 consecutive litters. Of 73 hearts preserved for morphological assessment, 52 were found to have defects within the ventricular septum, noticeably similar to those observed in humans with deficient ventricular septum. Three of these hearts showed evidence of spontaneous closure of pre-existing defects. The defects were perimembraneous in 34, being characterised by fibrous continuity between the leaflets of the tricuspid and aortic valves. These defects extended so as to open across the apical trabecular septum in six cases and toward the subpulmonary outlet in 28, though involvement of septal musculature was usually slight. Defects surrounded by muscle and opening to the subpulmonary outlet were found in 12 pigs. Defects characterised by absence of the outlet septum and fibrous continuity between the leaflets of the aortic and pulmonary valves (doubly committed juxta-arterial defects) were found in a further six hearts, two of which had fibrous continuity between the aortic and tricuspid valves, whereas the remaining four had muscular postero-inferior rims. Prolapse of the right coronary leaflet of the aortic valve was found in 14 hearts, eight with perimembraneous, two with muscular, and four with doubly committed defects. Atrial septal defects were found in 12 of the 52 hearts with deficient ventricular septation; only one atrial septal defect was seen among 21 hearts with an intact ventricular septum. Anomalies of the aortic arch were associated with ventricular septal defect in two cases, one with a solitary arterial trunk and one with hypoplasia of the aorta and patency of the arterial duct. All of these findings are replicated in human hearts.

This strain of pig, therefore, provides an ideal large animal model for morphologic and genetic investigations concerning the details of ventricular septation, including potential mechanisms of late spontaneous closure.

Effect of a new class III antiarrhythmic agent (UK 68 798) on QT interval and heart rate

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UK 68 798 (Pfizer) is a new class III antiarrhythmic agent that is devoid of subsidiary class I and II properties in animals. A study of the electrocardiographic effects of UK 68 798 at a range of intravenous doses was performed in 18 patients (mean age 55, range 42–65 years) admitted for diagnostic coronary arteriography. Three groups of four patients each received infusions of 1·5, 3, and 4·5 µg/kg over 10 minutes. UK 69 798 had no significant effect on heart rate, PR interval, or QRS duration. The mean QT interval increased by a maximum of 36 ms (9·4%), 52 ms (13·1%), and 83 ms (21·7%) at the three doses. Equivalent increases in QT_c were 9·7%, 9·6%, and 20·1%. Mean plasma concentrations at the end of infusion for the three doses were 1·74, 3·35, and 5·11 ng/ml. There was a linear correlation between the area under the plasma concentration/time curve and dose and between plasma concentration and change in QT_c. Mean plasma elimination half life was 8 7 h. The increase in QT interval had fallen to 4·6%, 2·9%, and 9·7% at 60 minutes after infusion. In a further six patients, however, a divided dose regimen giving two thirds over 15 minutes and the remainder over 45 minutes maintained stable QT prolongation over one hour. No adverse effects were noted in any patient.

UK 68 798 seems to be a specific class III antiarrhythmic agent that warrants further invasive electrophysiological evaluation.

Enhanced safety of a low energy non-arcing ventricular catheter ablation system compared with high energy defibrillator discharges

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A new system for low energy direct current (DC) cardiac ablation has recently been described. The effects of DC catheter ablation were compared in 22 pigs with two systems, a standard 7F electrode with defibrillator high energy (HE) shocks (100–150 J) and a capacitive waveform low energy (LE) system (25–30 J) with a 7F contoured tip electrode. Baseline haemodynamic measurements, left ventricular angiography, 12 lead electrocardiography, and electrophysiological stimulation studies were undertaken before delivery of single (HE, n = 5 pigs; LE, n = 5) or five (HE, n = 7; LE, n = 5) shocks to the left ventricle. Voltage and current were recorded. Survivors were restudied at four weeks, after which hearts were excised for histological examination. No chronic differences in left ventricular ejection fraction (LE 54·9% to 54·3%; HE 54·4% to 55·5%) or electrocardiographic findings were found. Mean (SD) values for HE were 2035 (298) V, 135 (26) J, 65 (33) A, and 35 (14) Ω and for LE were 2460 (302) V, 29 (4) J, 45 (17) A, 60 (19) Ω (differences significant, each at $p < 0.001$). The HE group sustained more postshock arrhythmias and more severe hypotensive episodes. No deaths occurred in the LE group, compared with five in the HE group (one perforation, one electromechanical dissociation, one asystole, two intractable ventricular fibrillation; $p < 0.01$, χ^2 test). One animal died at 24 hours. No sudden deaths occurred during follow up. Chronic lesions in the multiple shock groups, characterised by transmural fibrosis and wall thinning, were comparable in size for both systems (HE 6·5 (3) cm^2, LE 6·3 (3) cm^2. No significant mural lesions were observed in animals receiving single shocks.

The contoured tip electrode with a low energy capacitive shock produces similar sized myocardial lesions to conventional shocks, but with less trauma. This non-arcing system should enhance the safety margin for ventricular catheter ablation using DC shocks.

Time to termination of paroxysmal junctional tachycardia as a predictor of tachycardia suppression with antiarrhythmic treatment

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Prophylactic antiarrhythmic drugs for paroxysmal junctional tachycardia are usually selected empirically, and oral treatment is frequently unsuccessful as a result. Suppression of tachycardia at electrophysiological study is predictive of long term efficacy but is invasive and expensive. The aim of this study was to determine if the time to termination of tachycardia after intravenous drug treatment could predict the results of invasive tachycardia suppression studies. Tachycardia termination and subsequent reinduction was attempted on 54 occasions in 35 patients with inducible sustained junctional tachycardia with one of three antiarrhythmic drugs (flecainide 2 mg/kg, sotalol 1·5 mg/kg, disopyramide 2 mg/kg). All infusions were given over 10 minutes and restimulation was attempted 10 minutes after completion of the infusion. Tachycardia terminations were classified as early (< 5 minutes) or late (> 5 minutes). Tachycardias that did not terminate with drug treatment were terminated by ventricular pacing. Nineteen of the 54 tachycardias were terminated early (13/20 with flecainide, 5/20 with sotalol, and 1/14 with disopyramide). These arrhythmias were all successfully suppressed during subsequent attempts at reinduction. Nineteen tachycardias were terminated late: successful suppression was achieved in only 12 of these (2/5 with flecainide, 5/8 with sotalol, and 5/6 with disopyramide). Sixteen episodes of tachycardia were not terminated by drugs (2/20 flecainide, 7/20 sotalol, 7/14 disopyramide), and none of these arrhythmias were suppressed during subsequent reinduction attempts.

Early termination of paroxysmal junctional tachycardia by an antiarrhythmic drug is more likely to be followed by arrhythmia suppression than is late termination ($p < 0.05$) or failure of termination ($p < 0.001$).

Two forms of back up defibrillation for antitachycardia pacing in ventricular tachycardia

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The risk of fatal acceleration has limited the use of antitachycardia pacemakers in the treatment of ventricular tachycardia (VT). We report our experience with two forms of back up defibrillation in seven patients (mean age 57 (12) years, all men, five with ischaemic heart disease and two with dilated cardiomyopathy) with recurrent VT despite drug treatment that could be terminated by ventricular pacing. The mean VT rate was 168 (26) beats/min. Three patients, each with a single configuration of haemodynamically stable VT, had an antitachycardia pacemaker implanted with a single ventricular wire. Both detection and response modes were activated only by a magnet in a local accident and emergency department where external defibrillation was available. The patients were followed up for a mean of 16 (range 13–18) months and had a mean of six (range 0–9) episodes pace terminated. The mean time from onset of tachycardia to treatment is 25 minutes, and one patient's tachycardias did not last sufficient time (10–15 minutes) to present to hospital. Acceleration occurred once, requiring external defibrillation. Four patients had a device implanted via a thoracotomy capable of both antitachycardia pacing and internal defibrillation. Two had more than one configuration of VT and two had a previous cardiac arrest. The devices were programmed to detect and treat either slow VT with pacing or low energy direct current (DC) shock or ventricular fibrillation and fast VT with maximum energy DC shock. After a mean follow up of four (range 1–7) months, spontaneous VT was terminated by burst pacing a mean of nine (range 0–32) times. In one patient a one joule shock accelerated a spontaneous tachycardia and in two patients pacing accelerated an induced tachycardia. The accelerated rhythm was detected and terminated automatically by a full energy shock in all patients. One patient had spontaneous VF automatically defibrillated.

To conclude, these data further show that pacing termination of ventricular tachycardia by a device requires back up defibrillation. A casualty activated device had a lower capital cost and was simpler to implant, but the long delay to treatment means that it should not be used for haemodynamically unstable arrhythmias. Antitachycardia pacing for VT should therefore be combined in a device offering internal defibrillation.

Textured surface left ventricular assist devices continue to consume platelets after intermediate term implantation in the calf model

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Textured surface left ventricular assist devices (TSLVADs) have been developed with a view to permanent clinical implantation but have already been used as a short term bridge to transplantation. An essential requirement of such devices is a non-thromboembolic and haematologically stable blood contacting surface. In textured surface devices this occurs, to some extent, as blood constituents are attracted to form a strongly adherent coagulum with subsequent neointimal formation, thus avoiding the thromboembolic complications commonly associated with smooth surfaced devices. The haematological consequences of TSLVAD implantation were evaluated in 17 calves for up to four months. Attraction and deposition of blood cellular elements on to the device surfaces after implantation resulted in an increased plasma haemoglobin concentration immediately after the operation, a fall in platelet count to 25% of preoperative values by day 2, and a fall in red cell count to 65% after one week. Plasma haemoglobin values returned rapidly to normal and red cell numbers were normal within one month. Red cell survival measured at one month (n = 10) and three months (n = 3) after implantation were similar to preimplantation values. After the initial thrombocytopenia there was a rebound thrombocytosis which peaked after one week. Platelet concentrations then fell, reaching a plateau at about 65% of preimplantation values, where they remained. Platelet lifespan measured at one month (n = 10) was significantly decreased (mean (SE) days 3·01 (0·11) *v* 1·76 (0·15); $p < 0{\cdot}001$) and, although there was some improvement, remained so after three months (n = 4, 2·06 (0·47); $p < 0{\cdot}01$).

These longer term results have shown that the developing neointima, while remaining strongly attached to the TSLVAD surfaces, continues to be highly consumptive of platelets three months after implantation and that longer term evaluation is needed before these devices can be considered for permanent use.

Coronary reactivity to ergometrine: possible relation to accelerated coronary sclerosis in cardiac transplant recipients

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Severe coronary artery spasm can occur in orthotopic cardiac transplant recipients. To investigate the possible mechanisms and the relevance of coronary spasm to the subsequent development of coronary disease the response of the coronary arteries to intracoronary ergometrine maleate was studied in 10 patients who had undergone orthotopic cardiac transplantation and were shown to have normal coronary arteries at angiography. Ergometrine in doses of 1, 5, and 10 μg was injected into the left coronary artery followed by 2 mg of isosorbide dinitrate. Proximal coronary artery luminal diameters were measured by automated computed quantitative angiography of the left anterior descending (LAD) and circumflex (LCX) vessels. Five patients (responders) showed a dose-response curve to intracoronary ergometrine which was similar to that previously seen in non-transplant recipients (mean percentage diameter change (SE) −24·68 (1·93) for LAD, −24·06 (3·91) for LCX). The remaining five patients (non-responders) showed a virtually flat dose-response curve significantly different from that of the responders ($p = 0{\cdot}001$ for LAD, $p = 0{\cdot}013$ for LCX). Angiography after two years showed significant coronary disease in four of the five responders to ergometrine. In contrast, the five non-responders to ergometrine continued to have no detectable disease by angiography.

Fall in epicardial evoked T wave amplitude in cardiac allograft rejection

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The repolarisation phase of the surface electrocardiogram is usually a sensitive indicator of myocardial damage but has proved disappointing in the diagnosis of cardiac allograft rejection. To enhance sensitivity we have serially measured epicardial evoked T wave amplitude with an externalised Rhythmyx pacemaker system telemetered to a TP2 analyser in 13 patients (12 men, one woman, median age 49 (range 34–57) years) followed for 19 (14–26) days after transplantation. A total of 228 records were analysed. Rejection was defined on endomyocardial biopsy. During the study 18 of the 31 biopsy specimens showed evidence of rejection. One patient had no biopsy specimens showing rejection, seven had one, four had two, and one patient had three. After rejection was diagnosed patients received intravenous methylprednisolone for three days. In 11 patients the initial rejection episode was associated with a significant fall in the evoked T wave amplitude (from 1·3 (0·7–2·3) mV to 0·6 (0·5–1·8) mV; $p < 0\,005$) which began 2 (1–4) days earlier. One patient with uncontrolled diabetes had no change in T wave amplitude during the rejection episode. No fall in T wave amplitude occurred in the absence of rejection. In the patients with a negative subsequent biopsy specimen there was an increase in T wave amplitude to approach baseline (1·0 (0 7–1·8) mV). Patients with more than one positive biopsy specimen had no further significant change in T wave amplitude, which may be due to the ongoing rejection.

These results suggest a potential non-invasive method of detecting cardiac rejection which is both sensitive and specific for first rejection episodes.

Does transmitral pulsed wave Doppler reliably diagnose acute rejection in heart transplant recipients?

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Recent studies suggest that changes in pulsed wave transmitral Doppler (PTD) indices of diastolic function are early markers of acute rejection after orthotopic heart transplantation. We prospectively studied 30 patients (23 men, seven women) between 1–40 (median 5) months after transplantation with serial PTD studies using a simultaneous phonocardiogram. The 250 consecutive ultrasound studies were related to the concurrent biopsy results (Billingham classification). On each occasion the average values of 20 consecutive beats were determined for peak early diastolic velocity (E, m/s), peak late diastolic velocity at atrial contraction (A, m/s), E/A ratio, isovolumic relaxation period (IVR, ms), IVR% (percentage change in IVR from previous value), IVR/rr (heart rate corrected IVR), time velocity integral (TVI, cm), diastolic filling period (DFP, ms). For every Billingham classification the pooled average values (SD) of each parameter are presented. In addition intraobserver and interobserver variability were analysed over 200 individual beats in 10 different patients. Thus for each Doppler parameter the threshold for individual physiological change (beyond measurement variability) was calculated: E 5·6%; A/A 16·6%; IVR 8%; TVI 4·6%; DFP 3·9%. With these criteria we could assess in individual patients whether there was a true physiological change during an episode of acute rejection. Of the 250 observations, 42 were Billingham classification 0; the corresponding values were E 0·85 (0 24); E/A 2·12 (0·87); IVR 61 (17); IVR% 11 (50); IVR/rr 0·09 (0·03); TVI 14 (4); DFP 321 (84). In Billingham classification 1 there were 179 observations and their corresponding values were E 0·83 (0·24); E/A 1·96 (0 87); IVR 69 (17); IVR% 5 (29); IVR/rr 0·10 (0 03); TVI 15 (4); DFP 324 (118). In Billingham classification 2 there were 29 observations and their corresponding values were E 0·89 (0·22); E/A 2·09 (1·03); IVR 68 (18); IVR 5 (26); IVR/rr 0·10 (0·03); TVI 15 (4); DFP 302 (88).

Despite a low measurement variability, there is considerable overlap among patients without acute rejection (Billingham classification 0), those with infiltrates (Billingham classification 1, mild acute rejection), and those with infiltrates and myocytolysis (Billingham classification 2, moderate acute rejection). PTD could not distinguish between patients requiring specific rejection treatment (Billingham classification 2) and others, either at group level or in individual patients, and therefore could not diagnose acute rejection. This suggests that haemodynamic factors other than acute rejection alter diastolic function in these patients early after heart transplantation, obscuring the development of Doppler changes, formerly described as diagnostic of acute rejection.

Influence of donor heart ischaemic time on left ventricular contractility in heart transplantation: assessment by the conductance catheter

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Donor ischaemic time (from explantation to implantation) may have an important impact on left ventricular (LV) systolic performance after orthotopic cardiac transplantation. Accordingly, we studied 14 transplant recipients (mean 25 months after transplantation) divided into two groups according to ischaemic time (group 1 < 140 min, $n = 7$, mean (SD) 128 (10) min; group 2 > 150 min, $n = 7$, 178 (15) min) ($p < 0{\cdot}01$). LV contractility was assessed with a conductance catheter to generate LV end systolic pressure volume relations (Ees) over a wide range of loads generated by inferior vena caval balloon occlusion. Data were acquired under control conditions and during dobutamine infusion (3 μg/kg/min). No patient had angiographic coronary artery disease or rejection by right ventricular biopsy. No intergroup differences were noted for age, sex of donor and recipient, time since transplantation, and body surface area. Heart rates were similar in both groups (baseline: group 1 84 (5), group 2 85 (2) beats/min; dobutamine: group 1 100 (17), group 2 102 (13)) beats/minute. Patients in group 1 had higher baseline LV contractility (group 1 Ees 2·5 (1·0), group 2 Ees 1·1 (0·4); $p < 0{\cdot}01$) and a greater response to dobutamine compared with patients in group 2 (4·7 (1·9), 2·2 (09): $P < 0\,01$).

Thus, there is a direct relation between donor ischaemic time and long term LV systolic performance under baseline conditions and during β1 adrenoceptor challenge.

In vivo imaging of low density lipoprotein

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The non-invasive identification of atheroma would have important therapeutic implications. The biodistribution of low density lipoprotein (LDL) is important in identifying patients with lipid abnormalities. LDL plasma kinetics have been studied with radiolabelling, which is a standard technique. It has been found possible in animal models to image atherosclerotic plaques that have taken up the radiolabel. Initially standard iodine labels were used but more recently a method of labelling with technetium-99m has been described, which provides better imaging characteristics. Initial work in rabbits has shown in vivo images of rabbit aorta, with increased uptake in hypercholesterolaemic (Watanabe) rabbits compared with controls. In 10 human volunteers biodistribution of iodine-123 and technetium-99m labelled LDL was similar, with uptake initially in the blood pool then predominantly in liver and spleen and subsequent excretion in intestine. Blood clearance of technetium labelled LDL was faster than that of the iodine labelled LDL (55 (25) *v* 308 (158) at 80% of 5 minute sample, 285 (204) *v* 1328 (138) at 60%). In six patients with peripheral vascular disease asymmetrical femoral uptake was seen in five of them at the site of their angiographically shown obstruction.

This suggests that technetium labelled LDL is a suitable tracer to provide non-invasive quantitative biodistribution of LDL and may accumulate sufficiently in peripheral atheromatous plaque to allow in vivo imaging.

Application of magnetic resonance velocity mapping to mitral and pulmonary flow of healthy volunteers

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Transmitral and pulmonary venous flow are important indices in evaluating left ventricular diastolic function. Magnetic resonance velocity mapping was used to measure transmitral blood flow and pulmonary venous flow velocity in 20 healthy volunteers. Velocity measurement was acquired in an oblique plane parallel to the horizontal long axis of the heart. By the same technique quantitative blood flow was measured in planes perpendicular to the right and left lower pulmonary veins (RLPV, LLPV). Flow (ml/s) was calculated from cross sectional area (cm^2) and mean velocity (cm/s). Transmitral flow showed two positive peaks, one during early ventricular diastole and the other during atrial systole. Peak mitral flow velocity in early diastole was 68 (12) cm/s and in atrial systole 39 (10) cm/s and the ratio between the two was 1·9 (0·6). Pulmonary venous flow showed two positive peaks, one during ventricular systole and another in diastole. A small back flow during atrial systole was noticed. Peak systolic velocity in the right lower pulmonary vein was 41·3 (11) cm/s, peak diastolic velocity 36·0 (10) cm/s, and peak back flow velocity 12 (2) cm/s. The mean flow indices were 13·0 (3·8) ml/s/m^2 and 11·9 (2·6) ml/s/m^2 in the RLPV and LLPV respectively.

Magnetic resonance flow imaging provides a non invasive measurement of transmitral and pulmonary venous flow which is of clinical importance in evaluating various cardiac diseases.

Combined three dimensional intravascular ultrasound imaging and three dimensional flow presentation

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The clinical use of intra-arterial ultrasonic imaging in conjunction with angioplasty is rapidly approaching. We have developed a computer based imaging system for reconstructing three dimensional models from ultrasonic data acquired intraluminally with an 8F catheter mounted probe. We report an assessment of the accuracy of the system and present preliminary data on the combined presentation of three dimensional flow fields and three dimensional arterial images. Measurements made directly and from the computer reconstructions of multiple diameters in 10 hollow metallic and plastic phantoms (internal diameter 6–48 mm) were compared. After calibration, the direct and computed measurements correlated extremely highly ($r = 0·98$). For 10 in vitro arterial specimens direct measurement at known levels of histological section prepared without "pressure fixing" were made with an estimated error of 10%. Discrepancy between the direct and computed measurements of up to 12% was observed, again consistent with accurate ultrasonic measurement.

Knowledge of the three dimensional morphology of a vessel has enabled us to calculate theoretical three dimensional flow velocities based on calculations of the Navier-Stokes equation. The resultant flow fields are represented by colour mapping on the computer screen. Combining accurate three dimensional computer visualisation of the arterial wall and three dimensional flow information produces a powerful diagnostic tool.

Magnetic resonance imaging of pericardial disease

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Complete examination of the pericardium by established methods (computed tomography and echocardiography) can be difficult. Diagnosis of pericardial constriction often depends on invasive pressure measurements and malignant involvement may be only fully shown at operation or necropsy. We evaluated the use of magnetic resonate imaging in detecting pericardial disease, particularly in diagnosing pericardial constriction and malignant invasion. A total of 108 adults were examined in a 0·5 Tesla magnetic resonance scanner by electrocardiographic gated spin echo sequences. Appearances of the pericardium were defined in 16 normal volunteers, 59 patients with heart disease unlikely to involve pericardium (including 25 patients after operation), eight patients with catheter proved pericardial constriction, and 15 patients with pericardial effusions. In normal volunteers and patients with miscellaneous heart disease the pericardium was up to 3 mm thick and in the postoperative group it was up to 3·3 mm. The cardiac cycle did not affect these measurements. Patients with pericardial constriction had pericardial thicknesses of at least 3·3 mm. In patients with pericardial effusions magnetic resonance imaging showed malignant involvement of the pericardium better than alternative methods.

Magnetic resonance imaging accurately shows pericardial thickening and is a good predictor of pericardial constriction. It shows malignant involvement of the pericardium more clearly than alternative non-invasive methods.

Dobutamine magnetic resonance imaging in patients with coronary artery disease

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Magnetic resonance imaging is difficult during dynamic exercise, and this has limited its value in patients with coronary artery disease. With intravenous dipyridamole and cine magnetic resonance imaging we previously showed wall motion abnormalities in two thirds of patients in whom thallium defects were seen. To increase this sensitivity we have now used intravenous dobutamine, which increases myocardial oxygen demand and has the advantages of being administered by peripheral infusion, a short half life, and low arrhythmogenicity. Twenty two patients with stable angina underwent coronary angiography, thallium tomography, and cine magnetic resonance imaging. Images were acquired in three perpendicular planes before and after dobutamine, allowing direct comparison of perfusion and wall motion, which were graded in nine segments as normal, reduced, or absent. Twenty patients had coronary artery disease, of whom 19 (95%) had reversible perfusion defects after dobutamine. All 19 also had reversible wall motion abnormalities. The perfusion and wall motion defects corresponded closely in site and extent. The two patients with normal epicardial arteries also had corresponding wall motion and perfusion abnormalities. Chest pain occurred in 18 patients but was easily controlled by decreasing the infusion rate. Transitory arrhythmias were seen in eight patients but were insignificant. The average increase in double product with dobutamine was 34%, 57%, 87%, and 104% with 5, 10, 15 and 20 μg/kg/minute respectively.

We conclude that magnetic resonance imaging during dobutamine stress is safe, fesible, and well tolerated and that it may be possible to extend the clinical role of magnetic resonance in patients with coronary artery disease.

Assessment of regional myocardial ischaemia by a combination of nuclear imaging (^{99m}Tc-methoxyisobutylisonitrile) and monophasic action potential recordings

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Monophasic action potentials recorded from the surface of the myocardium provide a sensitive measure of early and localised myocardial ischaemia. The duration of the action potential shortens in response to ischaemia. The slow myocardial washout characteristics of ^{99m}Tc-methocyisobutylisonitrite (MIBI) permits injection of the isotope at a time and site distant from the imaging process. We combined ^{99m}Tc-MIBI myocardial perfusion imaging with recordings of left ventricular endocardial monophasic action potential to detect myocardial ischaemia induced by incremental atrial pacing. Sixteen patients (age range 40–73; 10 women) undergoing investigation for chest pain were studied. After routine coronary angiography a monophasic action potential recording catheter was inserted into the left ventricle and its position documented by biplane cinematography. Recordings were made during incremental right atrial pacing. Each pacing train was maintained for two minutes, thereby establishing steady state conditions. At peak paced heart rate 400 MBq ^{99m}TC-MIBI was injected intravenously. Myocardial perfusion single proton emission computed tomography (SPECT) was performed one hour later with rest SPECT obtained the following day (two day, two doses protocol). Thirteen patients had significant coronary artery lesions. Abnormal perfusion was identified in 45 out of 117 myocardial segments (sensitivity 83% and specificity 80%). Monophasic action potential recordings were obtained from areas with reversible perfusion defects in six patients and from areas of normal perfusion in another six. The extent of action potential shortening was significantly greater ($p < 0{\cdot}05$) for the recordings from the myocardial areas with reversible perfusion defects (28·6 ms per 100 ms decrease in cycle length) compared with normally perfused areas (23·5 ms).

^{99m}Tc-MIBI while proving an ideal agent for use in conjunction with cardiac catheterisation procedures, is effective in identifying perfusion defects with atrial pacing stress. In addition, electrical changes of ischaemia have been shown in areas of myocardium where perfusion defects exist.

Transcoronary alcohol ablation of the atrioventricular node

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Catheter ablation of atrioventricular conduction is accepted treatment for intractable atrial arrhythmias but disadvantages include modest success rates, right ventricular damage, and the need for general anaesthesia. A new technique of selective catheterisation of the atrioventricular nodal artery (AVNA) and embolisation with absolute alcohol was attempted in six patients. In two patients the AVNA was not clearly identified and could not be catheterised; these patients subsequently underwent electrical ablation. In four patients the AVNA was clearly visualised and all four patients underwent successful transcoronary ablation. The AVNA was entered with a steerable 0·013 inch wire and a 2·2F infusion catheter manipulated down a conventrional 9F angioplasty guiding catheter. A His bundle electrode provides an excellent visual target when engaging the AVNA. Position within the AVNA was confirmed radiographically, and infusion of ice cold saline produced temporary A-H block in all four patients. Immediate and to date persistent block then occurred after injection of 0·5 ml absolute alcohol in three patients who both had an expected minor rise in cardiac enzyme activities (peak creatine kinase (heart type) <50 IU, normal 0–20). One patient who had 1 ml alcohol injected developed a significant increase in enzyme activity (creatine kinase (heart type) 146 IU). Subsequent echocardiography showed normal systolic function. Three out of four patients had escape rhythms, which were all narrow complex, mean cycle length 1130 ms. Coronary artery spasm developed in three out of six patients before injection of alcohol and resolved immediately with intracoronary nitrate treatment.

Ablation of the atrioventricular node by alcohol embolisation is an attractive and feasible alternative in patients who would otherwise require conventional ablation.

Use of automatic implantable defibrillators in the United Kingdom

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Implanted defibrillators represent an important option in the treatment of ventricular arrhythmias. Such devices implanted in the United Kingdom up to January 1990 were surveyed. Forty-nine devices have been implanted in 40 patients, data being complete in 34 patients (mean age 53 (13), 28 men) with a mean follow up of 9 (10) months. Twenty-one patients had ischaemic heart disease, nine patients dilated cardiomyopathy, and four patients other disease. The arrhythmia was ventricular tachycardia in 21 (6%) patients, ventricular fibrillation in six (18%) patients and both in seven (21%), and 25 of the 34 (74%) patients had had a preimplant cardiac arrest. Drug treatment had failed in all patients and ablation had failed in four (transvenous in four patients and surgical in two of these). Mean ejection fraction was 31% (16%), median 25%. In the past 12 months 18 of the 34 (53%) patients had their first device implanted and the number of implanting centres increased from five to 10. All have been implanted via a thoracotomy with two eipicardial patches. Seventeen out of 40 (43%) patients had devices implanted with defibrillator only function, 14 (35%) had devices with back up pacing implanted, and nine (22%) had devices with combined antitachycardia pacing implanted in the past seven months. Successful termination of spontaneous arrhythmias occurred in 17 of the 34 (50%) patients with no failures. No patients have died.

Although the overall numbers are small, there has been a dramatic increase in both the number of devices and centres implanting in the past 12 months. This is probably due to the expanding capabilities of the devices increasing the proportion of patients with ventricular arrhythmias in whom such a device is the treatment of choice. In this high risk group (74% with previous cardiac arrest, mean ejection fraction 31%) it is encouraging that there have been no deaths.

Acute and chronic histological appearances in catheter mediated ventricular ablation by low energy and conventional defibrillator systems

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The histological effects of lower energy direct current ablation are not well described. This study compares the acute and chronic (four weeks) histological appearances of two DC catheter ablation systems in the pig. A standard 7F electrode with defibrillator high energy (HE) (100–150 J) shocks and a capacitive waveform low energy (LE) (25–30 J) source with a contoured tip 7F electrode were used to deliver endocardial left ventricular shocks in 22 pigs. The catheter electrode was placed on the left ventricular free wall. Single (HE, n = 5 pigs; LE, n = 5) or five (HE, n = 7; LE, (n = 5)) unipolar cathodal shocks were delivered. Surviving animals were restudied after four weeks, when the hearts were excised, fixed, and stained for detailed studies. Fifteen chronic lesions and six hearts with acute lesions were examined. One specimen was obtained at 24 hours. Transmural and endocardial fibrosis without chronic inflammatory cell infiltrates were seen with HE and LE lesions. No significant long term electrocardiographic or left ventricular angiographic correlates with extent and type of lesion were observed. Cartilage type and carbon deposits were absent in chronic lesions. A mitral leaflet haematoma and left ventricular aneurysm was observed after four weeks after multiple LE shocks in one animal. Macroscopically, acute lesions were poorly defined. Microscopically, acute lesions produced contraction band coagulation, interstitial haemorrhage, and haemosiderin pigment deposits. Pronounced nuclear alignment was observed after acute shocks without cellular disruption.

A fivefold reduction in ablation energy with a non-arcing capacitive waveform system produces comparable acute and chronic myocardial lesions with a conventional system in vivo. Differences in voltage, current, or energy may account for differing clinical but not histological effects.

Funding for implantable defibrillators in the United Kingdom: a comprehensive study

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In the past decade the use of implantable defibrillators has increased considerably throughout the world. All implanting centres in the United Kingdom have been surveyed, and though roughly 8000 devices have been implanted world wide, only 40 patients have received implantable defibrillators in the United Kingdom. Each device, including patches and sensing leads, costs about £13,000 plus the cost of implantation, and funding difficulties have been one factor limiting their use. The source of funding has been examined in all cases. None of the centres has been allocated a specific defibrillator budget either centrally or locally. Twenty patients had their devices funded from pacing budgets, nine were funded by the referring health district, three were funded from "one off" regional funds, three were paid for privately, two were funded out of hospital contingency budgets and two by charities, and one was bought from a combination of charitable funds and the pacing budget. Several patients waited in hospital for up to three months awaiting funding. Funding for replacement units is often uncertain. Nevertheless, 25 of the 40 patients (62·5%) have received their implants in the past 12 months, and the number of implanting centres has risen from five to 10. All patients are currently alive and well, and treatment has been effective in all.

Implantable defibrillators have been shown to be cost effective by others, and the treatment is now well established. Specific budgets should be established to allow this treatment to be offered to appropriate patients, most of whom have life threatening arrhythmias.

Low energy ablation of accessory pathways: use of test shocks and non-arcing shocks

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Catheter ablation has potential as an alternative treatment to surgery for the Wolff-Parkinson-White syndrome, avoiding sternotomy and cardiopulmonary bypass. It remains experimental because of uncertainty about success rates and the risk of cardiac rupture due to the high pressures produced from arcing and gas expansion at the catheter tip. We have devised a system that delivers shocks of low energy without arcing. Catheter ablation was considered in patients with accessory pathways undergoing electrophysiological study before planned surgery. Ablation was attempted in 12 patients (age range 11–78). The site of the accessory pathway was posteroseptal (PS) in six, left free wall (LF) in four, and right free wall (RF) in two. Test shocks of 5–15 J were delivered to the site of earliest atrial activation during tachycardia. There was no effect on accessory pathway conduction in five patients (two PS, two RF, one LF) and catheter ablation was abandoned. These patients went on to planned surgery. Further shocks of 15–25 J were delivered to the remaining seven patients in whom transient loss of accessory pathway conduction followed test shock delivery. Shocks were delivered outside the coronary sinus os in four (PS), inside the coronary sinus in one, from the mitral annulus in one, and between the mitral annulus and the coronary sinus in one, four to 24 shocks (mean five, mean shock energy 19 J) were delivered. There were no episodes of coronary sinus rupture, tamponade, or coronary artery spasm. The only complications were transient episodes of atrial fibrillation and secondary atrioventricular block. At follow up (mean 13 months) in the seven patients who underwent ablation there was no accessory pathway conduction in five and modified conduction in two. Five patients remain free of tachycardia and are not taking any drugs and two are symptom free taking previously ineffective medication.

Low energy test shocks may be useful in selecting successful sites for ablation. Repeated non-arcing shocks are effective and safe for the ablation of accessory pathways at low energies and without barotrauma. Initial clinical experience suggests that this method may be an alternative to surgery in some patients.

Surgery for medically refractory ventricular tachycardias: resection, implantable defibrillators, or transplantation?

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Since October 1984, 33 consecutive patients (mean age 56·5 years) have undergone elective surgery for ventricular tachycardias. Thirty were males. Twenty-three had map guided extensive endocardial resection (EER), seven had implantable cardioverter defibrillators (ICDs), and four underwent cardiac transplantation. In the EER group four had additional localised exclusion cryoablation to scarred papillary muscle and the septum was crossed to resect right ventricular scar in four. Twenty-two out of 23 had concomitant aneurysmectomy or coronary artery bypass grafting, or both. There was one operative death (4·3%) in a patient who required additional mitral valve replacement and aneurysmectomy. There were three late non-sudden cardiac deaths with no recurrence of ventricular tachycardia. Of 18 long term survivors, one developed recurrence shortly after EER and had an ICD implanted; one developed a new arrhythmia at one year which was controlled by drug treatment; 16 had no recurrence of ventricular tachycardia at a mean follow up of 35 months. All seven with ICDs are alive. The four transplant recipients are well at short term follow up (mean five months).

EER is the treatment of choice if the ventricular tachycardia is reproducible and not multimorphic. Although a low ejection fraction in itself is not a contraindication for EER, ICDs are generally reserved for those with poor ventricular function and relatively infrequent tachycardia who do not meet the constraints for EER. Transplantation is primarily indicated in those within accepted age limits if poor ventricular function is associated with frequent tachycardia.

Suprapulmonary stenosis in transposition of the great arteries after arterial switch operation

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The arterial switch procedure has been the operation of choice for transposition of the great arteries at our institution since 1977. This procedure was chosen to prevent postoperative complications such as arrhythmias and venous obstruction. Instead pulmonary trunk (PT) narrowing has become the main medium term complication for this condition. To assess this problem we studied 75 consecutive patients who underwent the arterial switch procedure (1977–89). Follow up included yearly Doppler echocardiographic evaluation, cardiac catheterisation (n = 8) when indicated, and magnetic resonance imaging (n = 12). Some degree of suprapulmonary stenosis developed in 39 patients (52%), of whom four had a direct anastomosis after an initial banding of the PT, six had a direct anastomosis alone, eight a "French technique" after initial banding of the PT, and 21 "French technique" alone. This narrowing varied from mild in 4 patients (1·4–2 m/s) to moderate in 20 patients (2–3 m/s) and severe in 15 patients (3–4 5 m/s), of whom 12 (30%) required reoperation to enlarge the PT. The location of the narrowing was supravalvar in 20 (51%), at the bifurcation in 13 (33%), and at the pulmonary branches in one (3%). In five (13%) the precise location could not be determined.

We conclude that suprapulmonary stenosis was a frequent postoperative complication (52%) in our population. Most of these were mild or moderate, and only a small group (16%) required reoperation. The majority of these stenoses (51%) occurred just above the pulmonary valve at the site of the anastomosis, but 33% occurred distally and seemed to be related to "stretching" of the PT during the "French" manoeuvre.

Options for surgical repair in hearts with univentricular atrioventricular connection and subaortic stenosis

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Thirteen patients underwent surgical treatment because of subaortic obstruction in hearts with a univentricular atrioventricular connection. Nine patients underwent surgical enlargement of the ventricular septal defect and four patients had construction of an aortopulmonary anastomosis and closure of the pulmonary trunk (The Damus-Kaye-Stansel procedure). Two patients undergoing enlargement of the septal defect and two having the Damus-Kaye-Stansel procedure also had a modified Fontan procedure. One patient had complete atrioventricular dissociation after direct enlargement of the ventricular septal defect that necessitated insertion of an epicardial pacemaker. One patient died within 30 days of the operation after enlargement of the defect and two patients after the Damus-Kaye-Stansel procedure. There was one late death, occurring in a patient who underwent enlargement of the ventricular septal defect. Ten patients subsequently underwent conventional cardiac catheterisation and angiography or transcutaneous Doppler flow studies, or both, to assess the relief of the subaortic obstruction. The result was satisfactory in all.

In the light of this experience, we now recommend direct surgical enlargement of the restrictive ventricular septal defect for relief of subaortic stenosis occurring with a univentricular atrioventricular connection to a dominant left ventricle as it seems to be haemodynamically effective with a low operative mortality and morbidity.

Determinants of long term growth after surgical repair of a large ventricular septal defect in infancy

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The ultimate growth potential of infants undergoing early corrective cardiac surgery is as yet unknown. This study examined the long term growth patterns of 46 otherwise normal infants who survived primary surgical repair of large ventricular septal defect before 7 months of age. All available patients and their families were asked to return for follow up measurement of weight, length, and head circumference. Each measurement was expressed in SDs from the mean for age based on established local values. At a mean of 6·0 years after operation the mean weight, length, and head circumference of 35 infants of normal birth weight were only marginally abnormal in comparison with the reference population (-0.4 SD, -0.1 SD, and $+0.5$ SD; $p < 0.02$, $p > 0.05$ and $p = 0.008$ respectively) and did not differ in any parameter from those of 44 normal siblings. Among 11 low birthweight infants, however, all three parameters remained highly abnormal at long term follow up, both in comparison with the reference population (-1.7 SD, -1.7 SD, and -0.9 SD; $p < 0.001$ for each) and in comparison with 22 normal siblings. Other than birth weight, only the severity of the preoperative growth disturbance for each parameter had an influence on late postoperative growth. Weight, length, and head circumference scores at six months after operation correlated significantly with those at latest follow up, and a significant correlation also existed between patient and mid-parental height scores.

Early repair of large ventricular septal defect results in near normal long term growth in normal birthweight infants. These results support a policy of early surgery in infants with large ventricular septal defect and poor growth due to congestive heart failure.

Continued treatment with prostaglandins after pulmonary valvotomy for pulmonary atresia with intact ventricular septum

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Pulmonary atresia with intact ventricular septum (PA) is widely treated by stabilising with E type prostaglandin (PGE), then performing pulmonary valvotomy with modified Blalock-Taussig shunt. We elected to perform pulmonary valvotomy alone while continuing PGE postoperatively in 11 neonates with tripartite right ventricle and good size pulmonary arteries. All received PGE_2 preoperatively, intravenously or orally, for one to 56 days (median 3 days). The median age at operation was four days. In six the diagnosis was made on echocardiographic criteria alone; five also had cardiac catheterisation. Open pulmonary valvotomy was performed by cardiopulmonary bypass in eight, inflow occlusion in three. PGE_2 was continued postoperatively. One infant died 18 hours postoperatively with low cardiac output and high right atrial pressure probably related to inadequate atrial communication. In two infants the oxygen saturation fell severely and a Blalock-Taussig shunt was performed within 18 hours. The eight others were given PGE_2 for 3–44 days (mean 19 days). Balloon valvuloplasty was performed in two and infundibulectomy in one during the first three weeks postoperatively. Ten survived and have been followed up for six to 36 months postoperatively; one had an outflow patch at 22 months, three others atrial septal defect closure at 18 to 24 months.

Infants with PA and tripartite right ventricle respond well to pulmonary valvotomy alone with continued post operative PGE treatment. Avoiding a shunt simplifies postoperative management.

Late arrhythmias after the Fontan procedure

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Arrhythmias are a problem in managing aging patients who have undergone the Fontan procedure. Between 1972 and 1989, 58 patients have had this operation performed at this hospital. Of these patients, 31 have had postoperative arrhythmia documented, although most of these arrhythmic episodes were transient or fatal (11 cases) immediately after operation. The incidence of arrhythmia was greater in patients operated on for double inlet single ventricle (14 out of 20 (70%)) than for tricuspid atresia (16 out of 35 (46%)). Twelve patients developed late arrhythmias three months to 17 years (mean onset 4·7 years) after operation; 12 developed atrial arrhythmias, three nodal rhythm, two ventricular tachycardia, and one complete heart block. Age, right atrial pressure, pulmonary artery pressure, and previous shunt surgery were not preoperative determinants of tendency to early or late arrhythmia. At cardiac catheterisation 1 to 8 years postoperatively, however, there were significantly higher mean right atrial pressures in those that developed late arrhythmias (16·1 mm Hg, compared with 11·0; $p < 0{\cdot}01$) and high pulmonary artery pressures (13·1 mm Hg, compared with 8·8 mm Hg; $p < 0{\cdot}01$). Eighty-four percent of cases of atrial arrhythmia in particular occurred in the context of significant right atrial to pulmonary artery obstruction, and of the 16 patients in the series requiring reoperation for such obstruction, 63% had documented atrial arrhythmia. The occurrence of junctional and ventricular arrhythmias did not correlate with any variable measured properatively or postoperatively.

Rhythm disturbance, in particular atrial arrhythmia, is encountered increasingly in survivors of the Fontan procedure, compromising cardiac function. In this context right atrial to pulmonary artery obstruction should be sought even if not clinically apparent.

Is a subpulmonary ventricle in a Fontan circulation a Trojan horse?

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The optimal Fontan circuit is still controversial. We measured cardiac output by Doppler echocardiography during graded submaximal (up to 1·5 W/kg) supine bicycle exercise in seven patients (mean age 12·8 (2·8) years) 6·8 (2·1) years after a Fontan with a valved right atrium to right ventricle connection and in 29 patients (age 12·8 (6·0) years) 4·7 (3·6) (years after a right atrium to pulmonary artery connection. Results were compared to age matched controls. Patients with a right atrium to pulmonary artery connection had a normal cardiac index at rest, but increases with exercise were smaller than normal ($p < 0{\cdot}05$). In contrast, patients with a right atrium to right ventricle had a lower cardiac index both at rest ($p < 0{\cdot}05$) and during exercise ($p < 0{\cdot}01$). Controls and patients with a right atrium to pulmonary artery connection increased their stroke volume (+19% (nine percent and (15%) (12%) respectively) with exercise but all patients with a right atrium to pulmonary artery Fontan had a fixed or decreasing stroke volume presumably due to the small, poorly compliant right ventricle incorporated in the circuit. Even the three patients with a right atrium to right ventricle Fontan who functioned as a biventricular heart (no antegrade pulmonary flow during ventricular diastole) were unable to increase their stroke volume with exercise. Age, time of follow up, or ventricular contractility (except when severely impaired) had no predictive value in a multivariate analysis.

The right atrium to right ventricle circuit is thus rate dependent and more vulnerable to the effects of tachycardia. This, together with the high incidence of conduit dysfunction-reoperation, argues against incorporation of a right ventricle in the Fontan circuit.

LETTERS TO THE EDITOR

RITA trial protocol

SIR,—The merits of a well controlled clinical trial for the assessment of a new treatment in clinical medicine are established. Statisticians and epidemiologists have increasingly laid down more stringent and exacting criteria for conducting these trials and this has led to more valid results and conclusions. Recently, however, there have been examples where the criteria necessary to fulfil the demands of the statistician have been such that the study population recruited no longer represents the intended population and consequently the relevant clinical questions have not been answered.

The randomised intervention treatment of angina (RITA) trial (1989;62:411–4) suffers from a major methodological error in that it imposes on one group of patients—the angioplasty population—a treatment strategy that is not generally practised by the physician performing the procedure. The surgical strategies for revascularisation and the strategies for angioplasty are quite different and it is these strategies that should be compared rather than the likelihood that angioplasty will achieve exactly what the surgeon would wish to achieve.

Coronary artery bypass surgery aims to revascularise all important vessels with lesions that are haemodynamically significant at the time of the procedure or that are thought likely to become so in the future. The strategy of angioplasty varies between operators, centres, and individual patients, but it aims to make the patient symptom free with a pattern of disease that has a good prognosis. Lesions that are not haemodynamically significant are frequently not dilated because of the possibility of inducing a significant restenosis. With angioplasty the operator can postpone treating these lesions and treat them only if they become haemodynamically significant. The surgeon, because of the "cost" of surgery to the patient, does not have this option and therefore has to revascularise all vessels with potentially significant lesions at the time of the initial procedure.

By forcing a treatment strategy on the physician performing the angioplasty that is not widely used and that favours the surgical arm of the trial, the result of the RITA trial, whatever the outcome, will have few implications for clinical practice. It is unfortunate that a large amount of effort and money is being spent on this trial that does not address the clinical problems relevant to coronary artery revascularisation and will not provide reliable information on which the future allocation of resources can be based.

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This letter was shown to Dr Henderson, who replies as follows:

SIR,—Several of the points raised by Dr Beatt were initially considered very carefully by the Protocol Committee of the RITA trial and his letter does not state the position correctly. Extensive surgical experience has shown the benefits of complete revascularisation and it was felt likely that the extent of revascularisation would also be important in patients treated by percutaneous transluminal coronary angioplasty. The angioplasty philosophy that only some of the important lesions need be dilated is not universally accepted and attempts to achieve complete revascularisation account for the tremendous increase in multivessel dilatations in the United States.

The RITA trial requires that the cardiologist and surgeon plan to achieve equivalent revascularisation. There is no commitment for the cardiologist to dilate subclinical lesions that would be grafted by the surgeon nor is there a commitment for the surgeon to leave subclinical stenoses ungrafted. For example the surgeon might decide to bypass two tight stenoses and an additional 50% stenosis in another vessel. The angioplasty requirement would be to dilate the two tight stenoses but not necessarily the 50% stenosis.

The question whether incomplete revascularisation by angioplasty can produce results that compare with complete revascularisation by coronary artery bypass grafting is being addressed by other trials, such as the Bypass Angioplasty Revascularisation Investigation (BARI) and the Coronary Artery Bypass Revascularisation Investigation (CABRI), and it has always been recognised that these trials favour the surgical arm.

It seems that Dr Beatt has misunderstood that subclinical lesions need not be dilated in the RITA trial and this results in his final comments.

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For the RITA Trial Executive Committee

Major complications of coronary arteriography: the place of cardiac surgery

SIR,—Stewart *et al* (1990;63.74–7) suggest that it may be more desirable to expand facilities at regional centres rather than devolve the investigation to district general hospitals, even though suitably trained cardiologists may practice there. Their study does not support this contention at all. It would be of interest to hear from the many hospitals already performing coronary angiography without cardiac surgery on site. Are these to be phased out because they are unsafe?

Indeed, several centres are performing not only coronary angiography but coronary angioplasty without on site facilities for cardiac surgery. Richardson *et al* recently reported the Belfast experience for percutaneous transluminal coronary angioplasty without on site facilities for cardiac surgery and concluded "With careful selection of patients coronary angioplasty may be safely performed in a hospital without on site cardiac surgery facilities, provided that these are available at a nearby centre."[1]

We are in an era of trying to improve the availability of cardiac investigations to increased numbers of the population but this demand cannot be met solely by the regional centres. To avoid unnecessary delay it seems reasonable for properly trained cardiologists to perform coronary angiography locally at district general hospitals provided the images obtained are of diagnostic quality. In my opinion this proviso is the limiting factor. A study is currently under way at Maidstone and Guy's Hospital and preliminary results suggest that coronary angiography at district general hospitals is safe, reliable, feasible, affordable, and diagnostic.

The debate will clearly continue as Mills suggested in his editorial in the *British Heart Journal.*[2] The outcome may revolutionise the practice of cardiology in the United Kingdom.

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1 Richardson SG, Morton P, Murthah JG, O'Keeffe DB, Murphy P, Scott ME. Management of acute coronary occlusion during percutaneous transluminal coronary angioplasty. experience of complications in a hospital without on site facilities for cardiac surgery. *Br Med J* 1990,300.355–8
2 Mills P Should coronary angiography be performed in district hospitals?. *Br Heart J* 1990;63.73.

Catheters or isotopes in the district general hospital?

SIR,—Stewart *et al* highlighted the potential problems of "routine" coronary arteriography performed without surgical cover (1990;63:74–7), and Mills has used their findings to fuel the debate about the safety of coronary arteriography in the district general hospital (1990;63.73). I believe that the debate is academic.

In patients with stable coronary artery disease diagnostic and therapeutic decisions can usually be made on the basis of the history, examination, electrocardiography, and non-invasive assessment of myocardial perfusion by thallium-201 or one of the newer technetium isonitriles.[1] But cardiologists who are unaware of the high quality of modern emission tomography feel the need to resort to coronary arteriography to be on safe ground. Non-invasive tests alone, however, can be used to decide who is at high risk of future cardiac events and could presumably benefit from intervention and who may continue on medical treatment.[2 3] Indeed, myocardial perfusion imaging is better than coronary arteriography for predicting outcome.[4] A knowledge of the coronary anatomy (as opposed to function) is needed only to guide the interventional cardiologist or the cardiac surgeon and therefore should be limited to the specialist centre. Here the decision to intervene has usually been made before referral and coronary arteriography cannot be avoided; but myocardial perfusion imaging remains important as an objective indicator of the site, extent, and depth of ischaemia.

Good quality nuclear cardiology is available only in a few district hospitals because many see it as a specialist technique that should be practised only in a specialist centre. The opposite is the case and the technique is most effective in aiding triage in hospitals without access to coronary arteriography.[5] Most districts do have access to nuclear medicine equipment but a recent survey showed considerable underuse of nuclear cardiology in the United Kingdom.[6] Only inertia and poor training in nuclear techniques can explain this

Some cardiologists dismiss these views as those of an enthusiast. It is true that enthusiasm is an important part of providing a reliable nuclear cardiology service, but those that doubt the effectiveness of non-invasive techniques forget that it is their unfamiliarity that limits the value of myocardial perfusion imaging and not the technique itself. Instead of ignoring it they should follow the practice of their colleagues who are able to manage patients with objective measurements of myocardial perfusion rather than subjective impressions of the severity of disease made from the coronary arteriogram. They might then find that they can make many therapeutic decisions without the need to reach for their catheters, and we shall be spared the debate about the role of cardiac catheterisation in the district general hospital.

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1 Steinberg EP, Klag MJ, Bakal CW, Strauss HW, Boucher CA, Guiney TE. Exercise thallium scans patterns of use and impact on management of patients with known or suspected coronary artery disease *Am J Cardiol* 1987,59 50–5.
2 Cerqueira M, Ritchie JL. Thallium-201 scintigraphy in risk assessment for ambulatory patients with chest pain· does everyone need catheterisation? *J Am Coll Cardiol* 1988, 12 35–6
3 Ladenheim ML, Pollock BH, Rozanski A, *et al* Extent and severity of myocardial perfusion as predictors of prognosis in patients with suspected coronary artery disease *J Am Coll Cardiol* 1986;3 464–71.
4 Kaul S, Finkelstein DM, Homma S, Leavitt M, Okada RD, Boucher CA Superiority of quantitative exercise thallium-201 variables in determining long-term prognosis in ambulatory patients with chest pain a comparison with cardiac catheterization *J Am Coll Cardiol* 1988,12 25–34.
5 Helfant RH, Klein LW, Agarwal JB Role of cardiac testing in an era of proliferating technology and cost containment. *J Am Coll Cardiol* 1987,9 1194–8.
6 Underwood SR, Gibson CJ, Tweddel A, Flint J Survey of nuclear cardiological practice in Great Britain in 1988 [Abstract] *Nucl Med Commun* 1989,10:258–9.

Acromegalic heart disease

SIR,—We disagree with several of the statements in the article by Rodrigues *et al* entitled "Subclinical cardiac dysfunction in acromegaly· evidence for a specific disease of heart muscle" (1989,62.185–94)

In the summary Rodrigues *et al* say that "This is the first study to find evidence of subclinical cardiac diastolic dysfunction in acromegaly", and in the discussion they say that "Left ventricular diastolic function has not previously been studied in acromegaly". I would like to draw attention to the paper of Bertoni and Morandi entitled "Impaired left ventricular diastolic function in acromegaly· an echocardiographic study", where relaxation abnormalities of the left ventricle were shown in acromegalic patients in 1987.[1]

On the basis of the paper by Lie and Grossman,[2] Rodrigues *et al* suggest that the fibrosis which is partly responsible for the diastolic filling disturbance is a consequence of an inflammatory process. Van den Heuvel *et al* took biopsy specimens of the right ventricle of an acromegalic patient and later examined specimens taken at necropsy. Both specimens showed the same changes hypertrophic myocardial fibres and some fibrous thickening of the endocardium There was no evidence of any inflammatory changes.[3] In rats with myocardial hypertrophy caused by tumours producing growth hormone Gilbert *et al* found direct evidence that there was no underlying inflammatory process [4]

These results prove that the main pathological background of acromegalic heart disease is left ventricular hypertrophy, with some contribution from myocardial fibrosis and the increased collagen content of the myocardium We found the dilated form of the disease in a few of our patients but not an inflammatory process; these patients were burned-out cases with lower serum concentrations of growth hormone than those with hypertrophy.[5]

Rodrigues *et al* cited the second edition of Feigenbaum's *Echocardiography* (not published in 1979 but in 1976) as saying that echocardiography is an insensitive method of assessing left ventricular function. However, this is not the opinion given in the fourth edition published in 1986.[6] Radionuclide ventriculography is probably a better method of assessing the ejection fraction than echocardiography. But because there are several other indices of left ventricular function (for example, enlargement of the left ventricle and segmental wall movement abnormalities) echocardiography cannot be deemed to be an insensitive method of evaluating left ventricular function [7]

In Rodrigues *et al*'s paper apart from 13 self-citations, there are only three references from 1982–84 and only one, an abstract, dated 1986 The references I cite were published between 1983 and 1987.

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1 Bertoni PD, Morandi G Impaired left ventricular diastolic function in acromegaly. an echocardiographic study *Acta Cardiol (Brux)* 1987,15:1–10.
2 Lie JT, Grossman SJ Pathology of the heart in acromegaly: anatomic findings in 27 autopsied patients *Am Heart J* 1980,100 41–52.
3 van den Heuvel PACMB, Elbers HRJ, Plokker HWM, Bruschke AVG Myocardial involvement in acromegaly *Int J Cardiol* 1984,6. 550–3.
4 Gilbert PL, Siegel RJ, Melmed S, Sherman CT, Fishbein MC. Cardiac morphology in rats with growth hormone-producing tumours *J Mol Cell Cardiol* 1985,17.805–11.
5 Csanády M, Gáspar L, Hõgye M, Gruber N The heart in acromegaly an echocardiographic study *Int J Cardiol* 1983;2 349–57.
6 Feigenbaum H *Echocardiography*. 4th ed. Philadelphia. Lea and Febiger, 1986.
7 Roelandt J, Sutherland GR, Hugenholtz PG. The 1980's renaissance in cardiac imaging the role of ultrasound *Eur Heart J* 1989,10. 680–4

This letter was shown to the authors, who reply as follows

SIR,—In reply to Csanády's letter we would like to make the following comments Bertoni and Morandi published a paper on left ventricular diastolic function in 1987,[1] but our study was largely completed in 1986 and was presented in part to the British Cardiac Society in December 1986.[2]

Csanády seems to disregard the seminal work on pathological findings of Lie and Grossman[3] in favour of the necropsy findings in a patient described by van den Heuvel *et al* [4] Necropsy findings in only one patient do not disprove the findings of a large study. Furthermore, in our study we tried to assess the influence of myocardial hypertrophy by studying left ventricular mass derived echocardiographically and showed that there was no correlation between peak filling rate abnormalities and left ventricular wall thickness or left ventricular mass. Therefore, it is unlikely that the abnormal peak filling rate seen in our patients was merely a reflection of hypertrophy.

Though we agree that echocardiography can be used not only to measure ejection fraction but also to assess the anatomical consequences of left ventricular dysfunction, such as left ventricular enlargement and wall motion abnormalities, the point we made in our discussion was that subtle changes in diastolic relaxation were shown better by radionuclide ventriculography Indeed, Feigenbaum[5] pointed out the drawbacks and pitfalls of calculating ejection fraction by cross sectional echocardiography and did not go into any detail about the assessment of subtle diastolic function by this technique. We referred to our previous validation studies in the text to establish the quantitative success and reproducible nature of the radionuclide technique for assessing subtle diastolic left ventricular dysfunction. Many methods have been used to study a large group of patients with a rare condition. Previous studies did not deal with the same questions, nor was thallium-201 imaging used to exclude obstructive coronary artery disease.[6] Thus our suggestion that radionuclide ventriculography is better than echocardiography for picking up subtle left ventricular diastolic dysfunction is valid

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1 Bertoni PD, Morandi G Impaired left ventricular diastolic function in acromegaly an echocardiographic study *Acta Cardiol (Brux)* 1987,15 1–10
2 Rodrigues EA, Caruana MP, Lahiri A, Nabarro JDN, Jacobs HS, Raftery EB Evidence of left ventricular relaxation abnormality in patients with acromegaly [Abstract] *Br Heart J* 1987, 57 72
3 Lie JT, Grossman SJ Pathology of the heart in acromegaly anatomic findings in 27 autopsied patients *Am Heart J* 1980,100 41–52
4 van der Heuvel PACMB, Elbers HRJ, Plokker HWM, Bruschke AVG Myocardial involvement in acromegaly *Int J Cardiol* 1984, 6 550–3
5 Feigenbaum H *Echocardiography* 4th ed. Philadelphia Lea and Febiger, 1986·154–5
6 Csanady M, Gaspár L, Hõgye M, Gruber N The heart in acromegaly an echocardiographic study *Int J Cardiol* 1983,2.349–57

Severe haemolytic anaemia after replacement of the mitral valve by a St Jude medical prosthesis

SIR,—The interesting case report by Feld and Roth (1989,62·475–6) of severe haemolytic anaemia after mitral valve replacement with a St Jude medical prosthesis highlights the difficulty in detecting mitral paraprosthetic leaks. Despite clinical evidence of mitral regurgitation in their patient, careful echocardiography with Doppler studies failed to detect any prosthetic abnormality and left heart catheterisation was required to show severe paraprosthetic regurgitation.

We found that transoesophageal echocardiography with a 5 MHz phased array transoesophageal transducer (HP 21362A)[1] was helpful in nine patients (mean age 58 years) with mitral prosthetic regurgitation. One of them also had severe haemolytic anaemia after the insertion of a 27 mm St Jude mitral prosthesis Mitral regurgitation was detected by transthoracic echocardiography, including Doppler studies and colour flow mapping, in only six patients. Transoesophageal echocardiography clearly showed paraprosthetic leaks in all six patients with a mechanical prosthesis and central leaks due to leaflet dehiscence in all three patients with a bioprosthesis. These results were confirmed by cardiac catheterisation or operation or both in five patients, with two patients proceeding to surgery on the basis of transoesophageal echocardiographic findings alone.

The evaluation of prosthetic mitral valve dysfunction by transthoracic echocardiography is limited by acoustic masking by the prosthesis, whereas the transoesophageal probe can be positioned directly behind the left atrium. The results of transoesophageal echocardiography of mitral prosthetic dysfunction correlate well with surgical findings.[2 3]

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1 Seward JB, Khandheria BK, Oh JK, *et al.* Transesophageal echocardiography: technique, anatomic correlations, implementation and clinical applications *Mayo Clin Proc* 1988;63·649–80
2 van den Brink RBA, Visser CA, Basart DCG, Duren JR, de Jong AP, Dunning AJ Comparison of transthoracic and transesophageal colour Doppler flow imaging in patients with mechanical prostheses in the mitral valve position. *Am J Cardiol* 1989;63.1471–4
3 Calafiore P, Stewart WJ, Lombardo H, *et al.* Transesophageal echocardiography in mitral prosthetic dysfunction: echo-surgical correlation [Abstract]. *J Am Coll Cardiol* 1989; 13(suppl A):69A.

Follow up of patients treated with balloon dilatation of the aortic valve

SIR,—Vogel *et al* (1989;62:148–53) used pressure differences measured invasively as peak to peak gradients and non-invasively by Doppler echocardiography as peak instantaneous gradients to evaluate the success of treating aortic valve stenosis by balloon dilatation. They used a regression equation obtained by comparing the results in 12 patients to correct Doppler gradients to the corresponding peak to peak gradients. There are several objections to this approach:

(a) Peak to peak gradients measured by catheterisation and peak instantaneous gradient measured by Doppler echocardiography are conceptually different and the use of regression equations to estimate one from the other is not reliable.[1] Large differences are frequently seen between these two types of gradient.[2 3]

(b) This difference is often considerable in patients with aortic regurgitation,[2] which was present in 60% of the patients in this study after the procedure.

(c) The peak instantaneous gradient is always higher than the peak to peak gradient.[3] The regression equation applied showed that the inverse was the case in the reported study, indicating less than perfect Doppler echocardiographic recordings.

If pressure gradients are used it is probably more appropriate to estimate either mean gradients or peak instaneous gradients, both of which can be measured invasively as well as by Doppler echocardiography. This eliminates the need for a regression equation.

The use of valve areas has been recommended for follow up of adult patients.[4] This is probably more important in children, in whom the absolute valve areas vary more than in adult patients. I recommend use of the continuity equation to calculate the valve areas according to Skjaerpe *et al*[5] using the actual transvalvar flow.

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1 Currie PJ, Seward JB, Reeder GS, *et al.* Continuous-wave Doppler echocardiographic assessment of severity of calcific aortic stenosis a simultaneous Doppler-catheter correlative study in 100 adult patients. *Circulation* 1985,71:1162–9.
2 Krafchek J, Robertson JH, Radford M, Adams D, Kisslo J. A reconsideration of Doppler assessed gradients in suspected aortic stenosis. *Am Heart J* 1985,110.765–73
3 Hegrenæs L, Hatle L. Aortic stenosis in adults. Non-invasive estimation of pressure differences by continuous wave Doppler echocardiography. *Br Heart J* 1985;54.396–404.
4 Vogel JHK, King SB III *Interventional cardiology. Future directions* St Louis CV Mosby, 1989:242
5 Skjaerpe T, Hegrenaes L, Hatle L. Noninvasive estimation of valve area in patients with aortic stenosis by Doppler ultrasound and two dimensional echocardiography *Circulation* 1985,72:810–8

This letter was shown to Dr Benson, who replies as follows:

SIR,—Dr Dag Teien's comments prompted us to review our study and we agree with him that peak to peak gradients are poor reflections of instantaneous gradients across the stenosed aortic valve.[1] The instantaneous gradient generally does overestimate the peak to peak gradient. Our regression equation was obtained at the same time as direct measurements of aortic and left ventricular pressures in the catheterisation laboratory. Upon reflection, it has become clear to us that under these conditions alterations in pressure and flow dynamics, systolic ejection times, and arterial compliance can influence the contour of the upstroke of the aortic pressure curve in such a way as to have the peak to peak gradient approach the instantaneous gradient. We no longer use the regression equation to correct the pressure gradient estimate.

Because we did not find depressed pump function in children with aortic stenosis we still regard the left ventricular to aortic gradient as clinically useful in decision making. This view is supported by the studies of the course of untreated aortic stenosis[2] in the paediatric patients in which peak to peak gradients rather than valve areas were used for assessment. Furthermore, from infancy to adolescence valve areas change considerably, in a non-linear way, which additionally complicates estimating a normal valve area for a given patient

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1 Gordon JB, Folland ED Analysis of aortic valve gradients by transseptal technique, implications for noninvasive evaluation. *Cathet Cardiovasc Diagn* 1989;17 144–51.
2 Wagner HR, Ellison RC, Keane JF, Humphries J, Nadas AS Clinical course in aortic stenosis. *Circulation* 1977,56:I-47–I-56.

BOOK REVIEWS

Electrocardiography of Arrhythmias. Charles Fisch. (pp 451; £34.03.) Philadelphia and London: Lea and Febiger, 1990. ISBN 0-8121-1265-2.

Does the surfeit of books on basic electrocardiography—introductions, primers, guides and the like—tell us that the subject is unduly difficult to comprehend? Perhaps it is too much taken for granted or possibly ignored by teachers; certainly in the United Kingdom, the home of Waller and Lewis two of the founding fathers, this seems to be so. We have no tradition of the "heart station" with reporting of tracings as a regular feature of hospital life and thus less opportunity for the watching student to learn the practical side of reporting from a mentor.

The European masters did know their fundamentals, however, though many had to make their way to the United States in the years encompassing the second world war. A happy liaison then developed between the rising expert on arrhythmias at the Michael Reese Hospital in Chicago, Louis N Katz, and two immigrants from Prague, Richard Langendorf and Alfred Pick. From them came a succession of papers and books on arrhythmias that have become classics. And now we have a major contribution from one of their foremost disciples and colleagues, Charles Fisch of Indianapolis. Dr Fisch is particularly well known for the courses he conducts at his Krannert Institute; but his programme on advanced arrhythmias on the Sunday before the annual meeting of the American College of Cardiology has brought him to the attention of many more who crowd into the lecture theatre to learn from his incisive analyses carried out in the form of a dialogue with members of a team to whom he shows complex tracings.

Now he has assembled and analysed representative selections from his extensive collection of material in the form of this book. It is not for the beginner, who might be better advised to have at hand and consult something like Dunn and Lipman's *Lipman-Massie Clinical Electrocardiography* (which also reflects the approach of the Chicago school) as well as a recommended introductory text. What Fisch does provide is an essential code book that explains concepts and phenomena which must be understood if the electrocardiographic analysis of arrhythmias—simple as well as complex—is to be more than the memorisation of some patterns.

Here we find descriptions of events that influence the electrocardiogram in classic, important, but too often poorly comprehended ways. The chapter headings indicate that this is no ordinary book that starts at the sinus node and ends with the recovery of the ventricles. They show the reader what is so often missing from the more conventional texts· careful descriptions of, for example, concealed conduction, aberration, and entrance and exit block that make possible understanding of what otherwise seems so difficult to sort out.

Although the text is liberally explained by well annotated examples of conventional electrocardiographic tracings, the author does not hesitate to use intracardiac recordings and monophasic action potentials to assure the validity of his explanations Citation of references is meticulous and deals appropriately with contemporary sources while not neglecting proper mention of those who first observed and elucidated specific findings. Production is of corresponding quality, the illustrations are clear, and the index is accurate and helpful Charles Fisch's book is an important contribution to the better recognition of arrhythmias by those who use standard electrocardiographs and is likely to remain an essential tool for all who read tracings showing rhythm disturbances.

DENNIS M KRIKLER

Diseases of the Heart. Eds Desmond G Julian, A John Camm, Kim M Fox, Roger J C Hall, and Philip A Poole-Wilson. (pp 1709, £55 00) London. Bailliere Tindall, 1989. ISBN 0-7020-1260-2.

Written and edited by master clinicians, this book has a uniform tone—a difficult achievement with more than 62 contributors. As stated in the preface, the editors' guide was Paul Wood's text which "combined lucidity with erudition". The objective seems to have been realised because *Diseases of the Heart* is readable but still learned.

Some texts are so coldly objective that they might have been written by non-clinical scientists; not so *Diseases of the Heart*. It is obvious that the contributors are clinicians with considerable experience and clinical acumen The text for the most part is not overburdened with reference numbers though the density of references is variable. The impression is of a well considered and balanced viewpoint rather than just a review of published reports The chapter on chronic heart failure by Professor Philip Poole-Wilson is a particularly good example of this. The chapter on angioplasty is another example of the approach of the experienced teacher-clinician—Dr M F Shiu has been there He may even have introduced a new word—disobliteration

There is a great deal more drug information in *Diseases of the Heart* than is usual for standard textbooks. That is a plus. It is somewhat distracting, however, to need to refer quite so frequently to the Appendix, where a brief and useful description of some commonly used cardiovascular drugs is tabulated. Perhaps too much effort was made to avoid repetitiveness by reference to the Appendix rather than by including the material in the relevant chapter. For example, when the use of verapamil in atrial flutter is described it would be useful to read (on the same page) the contraindications, precautions, and drug interactions that should come to mind. Though some cautions are given later when the drug's use for supraventricular tachycardias is discussed, the presentation of drug information in the text is somewhat uneven

The chapters on non-invasive diagnostic and evaluative technologies are excellent Magnetic resonance imaging and computed tomography are made as readily understandable as possible. Other technologies are also well covered. The chapter on exercise testing is particularly well done in terms of the usefulness of the test in clinical decision-making. Once again, it is the teaching approach that makes the difference.

To assess the usefulness of *Diseases of the Heart* as a practical clinical reference book, I used it on general cardiology teaching rounds for one month, looking up every patient problem as it presented. In almost all cases the material contained in *Diseases of the Heart* was relevant to the management of the patient in question and provided practical guidance Relevant information about conditions that are encountered less frequently could also be found in most cases The scope of the text is comprehensive without being overwhelming

The illustrations are generally good, the print easy to read, and the indexing adequate. Some of the electrocardiograms have been "touched up". For the purist this is somewhat distracting. But if the teaching points are made clearer, the end may justify the means.

Diseases of the Heart is a good and useful text with a strong clinical orientation. The editors achieved all their goals except for one. It is still a heavy book and not exactly "easier to handle". But there is a lot of material to cover, probably more than when Paul Wood's *Diseases of the Heart and Circulation* was written; some might question whether essential and clinically relevant knowledge has increased to the same degree as the size of our texts Paul Wood compressed large amounts of information to achieve clinical relevance and readability. *Diseases of the Heart* comes as close to replicating his style as any currently available text. Medical students, house officers, and practitioners should all benefit by the experience and insight of the authors of this text.

SUZANNE B KNOEBEL

NOTICES

British Cardiac Society page

The British Cardiac Society has become progressively more active in recent years under the guidance of its council and of successive presidents. I am sure this trend will continue. We have much to do. The problems that face us in 1990 are manifold and impinge on all of us.

The revision of the National Health Service under the terms of the white paper is taking us into uncharted territory which we may regard with apprehension but cannot avoid Technological advances offer increased prospects of reducing the mortality and morbidity of heart disease, but many patients do not benefit from new treatments because we have too few cardiologists struggling to maintain a service with resources that increasingly fail to match demand. The pattern of training for our registrars is being revised, with disagreement between those who want faster progression to consultant status and others of us who believe that training programmes must offer sufficient experience in cardiology to produce specialists regarded as competent both here and throughout Europe. The momentous changes in our continent will provide opportunities and challenges that we must be able to meet. But closer liaison in the political arena is accompanied by more diversity professionally, with the risk of fragmentation of interest, as we are all driven to increasing specialisation. Finally, in our country more than most, academic cardiology—and academic medicine in general—feels under siege and must be supported.

In these difficult and exciting times the Cardiac Society must become a more important focus for our activities. From within the society we must learn to communicate more effectively The officers and the council will want to keep members well informed of their activities and to be responsive to the opinions of all our colleagues in the specialty. We will explore ways of achieving these twin goals, but I hope that one method will be by making more use of our own journal. The editor has agreed to a British Cardiac Society page.

As your president I want to be responsive as well: to new ideas from members, to criticisms, and to requests for help or advice which I can direct appropriately when I cannot address them myself I hope members will feel free to contact me as often as they feel the urge to do so. The path, I recognise, will not always be smooth. There is a great recipe for avoiding trouble—called inactivity. Neither I nor the council will follow it, and I do not think that you would want us to do so.

DOUGLAS CHAMBERLAIN
President, British Cardiac Society

British Cardiac Society

The Annual Meeting will take place at the Scottish Exhibition Centre, Glasgow, on 30 April to 3 May 1991.

Cardiopulmonary emergencies

The 6th International Symposium on Cardiopulmonary Emergencies will take place in Rotterdam on 26 to 29 November 1990 Inquiries to Dr Omar Prakash, Thorax Centre, Erasmus University, 3000 DR Rotterdam, The Netherlands Telephone: 31-10-463 5230. Fax 31-10-463 5240.

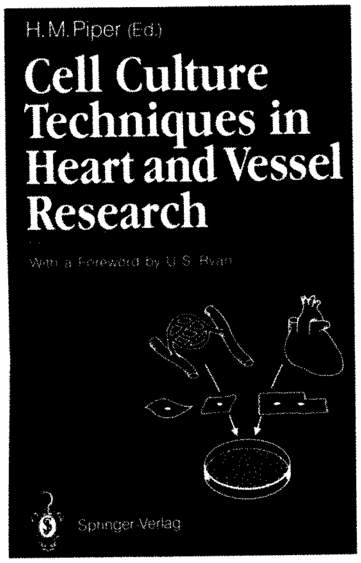
Coronary arteriography

The 4th International Symposium on Coronary Arteriography will take place in Rotterdam on 23 to 25 June 1991. Further information from Hoboken Congress Organisation, Erasmus University Rotterdam, PO Box 1738, 3000 DR Rotterdam, The Netherlands. Telephone: 31-10-408 7881/2 Fax· 31-10-436 7271.

Echocardiography

The 9th Symposium on Echocardiography will take place in Rotterdam on 26 to 28 June 1991. Further information from Hoboken Congress Organisation, Erasmus University Rotterdam, PO Box 1738, 3000 DR Rotterdam, The Netherlands. Telephone 31-10-408 7881/2. Fax: 31-10-436 7271

Keep up to date in Cardiology


H. M. Piper (Ed.)
Cell Culture Techniques in Heart and Vessel Research
With a Foreword by U. S. Ryan
Springer-Verlag

H. M. Piper, University of Düsseldorf (Ed.)

Cell Culture Techniques in Heart and Vessel Research

1990. XIV, 362 pp. 73 figs. 19 tabs.
Hardcover DM 176,- ISBN 3-540-51934-3

This book meets the demand for a comprehensive and easily accessible source for cell culture methods in cardiovascular research as was not previously available.
The basic methods for cultures of cardiomyocytes (embryonic and adult), endothelial cells (micro- and macrovascular), smooth muscle cells and pericytes are described in detail by an international selection of experts. Special chapters discuss the use of growth factors and attachment substrates, techniques for co-cultures, cultures on permeable filter membranes and microcarrier cultures. The methodological descriptions are sufficiently detailed for immediate application in the laboratory. All chapters also contain a critical evaluation of alternative approaches.

J.-P. Camilleri, C. L. Berry, J.-N. Fiessinger, J. Bariéty (Eds.)

Diseases of the Arterial Wall

1989. XXIX, 693 pp. 333 figs.
Hardcover DM 650,- ISBN 3-540-17492-3

This text combines extensive coverage of normal structure and function of the arterial wall with detailed accounts of the changes that occur in disease. These data are presented in a comprehensive way not found elsewhere; they are essential for the proper understanding of arterial disease and for its investigation using modern methodology.

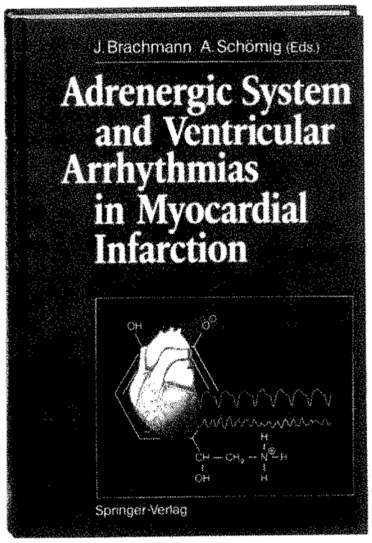
Distribution rights for Japan:
Igaku Shoin, Tokyo

J. Brachmann, A. Schömig,
University of Heidelberg (Eds.)

Adrenergic System and Ventricular Arrhythmias in Myocardial Infarction

1989. XIII, 363 pp. 126 figs. 14 tabs.
Hardcover DM 126,- ISBN 3-540-50593-8

This book presents new aspects of electrophysiological mechanisms and catecholaminergic contributions in the setting of acute and chronic myocardial ischemia. Special emphasis is placed on the full scope from basic molecular and cellular mechanisms to experimental models of close clinical proximity.
Contents include release and uptake of catecholamines in ischemia, regulation of receptors, adrenergic contribution to ventricular arrhythmias and mechanisms of ischemic malignant arrhythmias as well as underlying changes in membrane currents and the electrophysiological response to beta-adrenergic blocking drugs.


J. Brachmann A. Schömig (Eds.)
Adrenergic System and Ventricular Arrhythmias in Myocardial Infarction
Springer-Verlag

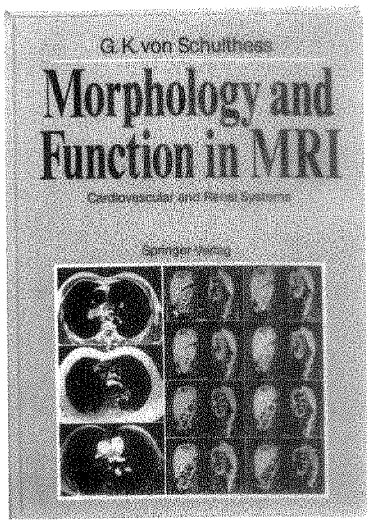
R. W. Jelliffe, University of Southern California, Los Angeles

Fundamentals of Electrocardiography

1990. X, 214 pp. 191 figs. Softcover DM 90,-
ISBN 3-540-97185-8

This well-written, up-to-date book provides a succinct account of the basic aspects of electrocardiography. It is intended for the resident or medical student seeking an understanding of the physiology of the ECG.

Prices are subject to change without notice.


G. K. von Schulthess
Morphology and Function in MRI
Cardiovascular and Renal Systems
Springer-Verlag

G. K. von Schulthess, University of Zurich

Morphology and Function in MRI

Cardiovascular and Renal Systems

With a Foreword by W. A. Fuchs and A. Margulis

1989. XV, 144 pp. 155 figs. in 273 sep. illus.
Hardcover DM 168,- ISBN 3-540-19061-9

Two systems which already demonstrate the advantages of MRI are presented. In the cardiovascular system, motion and flow can be imaged so that even flow velocities in the deep vessels of the body can be measured, and turbulences can be identified. In the study of the kidneys, a combination of renally excreted contrast media and imaging provides within seconds insight into glomerular filtration in health and disease.

A. S. Kapoor, University of Southern California, Los Angeles (Ed.)

Interventional Cardiology

1989. XVII, 415 pp. 135 figs.
Hardcover DM 180,-
ISBN 3-540-96783-4

Gives you practical guidelines to interventions, describing procedures involving modern technology and drugs with emphasis on the "how-to" aspects. The indications, techniques, results and merits of each procedure are given.
These include: coronary angioplasty and angioscopy, valvuloplasty, lasers and cardiac transplantation as well as basic procedures such as cardiac catheterization, electrophysiologic studies and automatic implantable defibrillators.

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Tenif

Try counting on 'Tenif' for effective angina control

PRESCRIBING NOTES FOR 'TENIF'

PRESENTATION
50mg atenolol +20mg nifedipine.

DOSAGE

MANAGEMENT OF HYPERTENSION – Orally one capsule daily; recommended where therapy with either a calcium channel blocker or a beta-blocker proves inadequate. If necessary one capsule twice daily.

MANAGEMENT OF ANGINA – One capsule twice daily, recommended where therapy with either a calcium channel blocker or beta-blocker proves inadequate.

CHILDREN – Not recommended.

ELDERLY PATIENTS – Dosage should not exceed one capsule daily in hypertension or one capsule twice daily in angina.

CONTRA-INDICATIONS
Heart block, cardiogenic shock, overt heart failure, women of childbearing potential, lactation. Co-administration with cardiodepressants e.g. verapamil.

PRECAUTIONS
Untreated cardiac failure, bradycardia, anaesthesia. Caution in patients with chronic obstructive airways disease or asthma. Withdrawal of beta-blocking drugs should be gradual in patients with ischaemic heart disease. Withdrawal of clonidine. Co-administration with Class I antidysrhythmic agents. Interactions with cimetidine or quinidine.

Diabetes: Diabetic patients receiving 'Tenif' may require adjustment of their diabetic therapy. Modification of the tachycardia of hypoglycaemia may occur.

Hepatic or renal impairment: In patients with marked renal impairment (i.e. creatinine clearance below 15ml/min/1.73m^2, serum creatinine greater than 600 micromol/litre) the use of 'Tenif' is considered inappropriate. Care should be taken in patients with marked hepatic impairment.

SIDE EFFECTS
Headache, flushing, fatigue, dizziness and oedema may occur. Skin rashes and dry eyes have been reported with beta-blockers – consider discontinuance if they occur. Rare reports of jaundice and gingival hyperplasia with nifedipine.

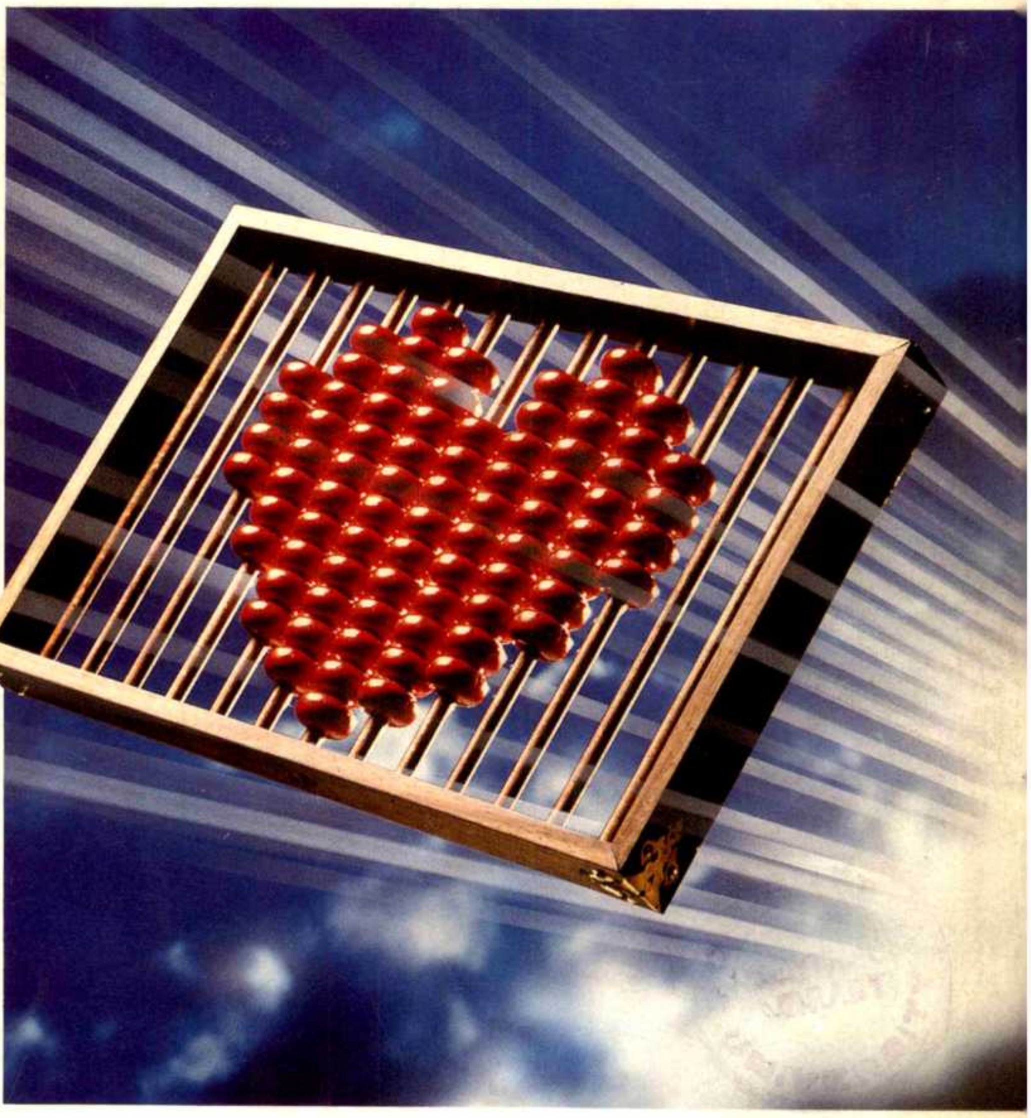
PRODUCT LICENCE NUMBERS AND BASIC NHS COST:
'Tenif' Capsules 29/0202, 29/0216 in calendar packs of 28, £10.90.

A data sheet is available and should be consulted before prescribing.

'Tenif' is a trade mark.

Further information is available on request from the Company.

STUART
Stuart Pharmaceuticals
Stuart House, 50 Alderley Road
Wilmslow, Cheshire SK9 1RE



For patients for whom the recommended dose of nifedipine proves inadequate . . .

330

1 b.d. in angina

Tenif

atenolol 50mg, nifedipine 20 mg

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BRITISH HEART JOURNAL

In association with the British Cardiac Society

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NOTICE TO CONTRIBUTORS

Papers relating to the heart and circulation should be sent in triplicate to the Editor, British Heart Journal, BMA House, Tavistock Square, London WC1H 9JR, and be prepared according to the *Uniform requirements for manuscripts submitted to biomedical journals* (Vancouver agreement) (*Br Med J* 1988;**296**:401–5). Authors are asked to complete a copy of the checklist provided (1990;**63**:71–2 (January issue)) when submitting their manuscripts for publication. The reference number given on the acknowledgement postcard sent out by the editorial office should be quoted on all subsequent correspondence and telephone inquiries. A covering letter must be signed by all authors stating that they have seen and approved the paper and that the work has not been, and will not be, published elsewhere. All authors will be required to transfer copyright of their articles to the journal before publication. (All material for possible publication (including Letters to the Editor) *must* be typed in *double spacing* with 4 cm margins.)

ETHICAL STANDARDS

Authors are expected to comply with the code of ethics known as the Declaration of Helsinki. Where appropriate, manuscripts should include a statement that the research protocol has been approved by the locally appointed ethics committee and that the informed consent of the subjects has been obtained.

CASE REPORTS should convey only the essential facts of a case and the discussion and bibliography be kept to a minimum. They should have no more than three authors, should not exceed 1500 words, and include no more than two Figures.

ABBREVIATIONS should *not* be used in the text, except for mathematical calculations and units of measurement.

REFERENCES must be cited precisely according to the Vancouver agreement and be typed in *double spacing*. As a general rule, no more than three references should be cited for any one statement.

Authors are responsible for the accuracy of any references cited: these should be checked at source or with the listing in Index Medicus.

UNITS OF MEASUREMENT

All haematological and clinical chemistry measurements should be given as SI units. Blood pressures should be given in mm Hg. Measurements of length, height, weight, and volume should be reported in metric units and temperatures should be reported in degrees Celsius.

TABLES must be typed on separate sheets and not in the text. Titles should be provided, and all abbreviations used must be given in full in a footnote.

ILLUSTRATIONS (for general requirements, please refer to *Br Heart J* 1984;**51**:1–6).

Electrocardiograms: Black and white prints only should be sent and not the original tracings. If several tracings are grouped in a single Figure only a few complexes should be shown; the width should not exceed 14 cm unless a reduction in scale is possible.

Echocardiograms: All unnecessary or irrelevant detail (such as electronic writing) should be removed. Labelling must be superimposed directly on to the print itself and only where essential be shown on an accessory drawing. Echocardiograms obtained with 30° sector scans or bistable equipment or recorded on ultraviolet paper are not suitable for publication.

Figure legends must include an explanation of all abbreviations used in the Figure.

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PROOFS of articles accepted for publication will be sent for the author's approval. Proof corrections should be kept to a minimum.

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Name one other antihypertensive with this in its data sheet...

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Indications: First-line treatment of hypertension and may be used as the sole agent to control blood pressure in the majority of patients, including those with asthma, gout and the elderly. **Dosage:** Cardura* is used in a once daily regimen. The initial dose is 1mg. Dosage may then be increased after 1 or 2 weeks of therapy to 2mg and thereafter, if necessary, to 4mg. The majority of patients who respond to Cardura will do so at a dose of 4mg or less. Dosage can be further increased, if necessary, to 8mg or the maximum recommended dose of 16mg. **Use in children:** Not recommended. **Contra-indications:** Sensitivity to Cardura and related quinazolines. Lactation. **Use during pregnancy:** Cardura should only be used during pregnancy when, in the opinion of the physician, potential benefit outweighs potential risk. **Side effects:** Postural hypotension, rarely associated with fainting. Other reactions include: dizziness, vertigo, headache, fatigue, asthenia and oedema.

Further information: **In short-term studies, Cardura produced a modest reduction in plasma total cholesterol and LDL cholesterol.** **Basic NHS Cost:** 1mg tablet (PL 57/0276) Calendar pack of 28, £9.60; 2mg tablet (PL 57/0277) Calendar pack of 28, £12.80; 4mg tablet (PL 57/0278) Calendar pack of 28, £16.00. *Trade Mark. Further information on request. Invicta* Pharmaceuticals. A division of Pfizer Limited, Sandwich, Kent CT13 9NJ.

INVICTA PHARMACEUTICALS

55282

ABRIDGED PRODUCT INFORMATION

Refer to Data Sheet before prescribing.

INDICATIONS

Primary hypercholesterolaemia, intolerant or not responsive to other forms of therapy, with a cholesterol level in excess of 7.8 mmol/litre.

DOSAGE AND ADMINISTRATION

Initially 10 mg *nocte*; dose range 10-40 mg once daily *nocte*. Maximum therapeutic response occurs within four to six weeks. Consider dose reduction if total serum cholesterol level falls below 3.6 mmol/l or if LDL cholesterol falls below 1.94 mmol/l. (See Data Sheet for full dosage instructions.) A standard cholesterol-lowering diet should be continued. *Concomitant therapy:* 'Zocor' is effective alone or in combination with bile-acid sequestrants. *Impaired renal function and elderly patients:* Modification of dose should not be necessary. *Children:* Studies to show safety and efficacy have not been done.

CONTRA-INDICATIONS

Hypersensitivity to this product; active liver disease or unexplained persistent elevations of serum transaminases; pregnancy and breast-feeding; women of child-bearing potential unless adequately protected by non-hormonal methods.

PRECAUTIONS

Homozygous familial hypercholesterolaemia: 'Zocor' is unlikely to be effective. *Hypertriglyceridaemia:* 'Zocor' is not indicated where hypertriglyceridaemia is the abnormality of most concern. *Hepatic effects:* Initial and periodic liver function monitoring recommended. Discontinue if persistent enzyme elevations occur, particularly if they rise to three times the upper limit of normal. Caution in patients with a history of liver disease and/or alcoholism. *Muscle effects:* Clinically insignificant transient mild elevations of creatine-phosphokinase may be seen. Therapy with 'Zocor' should be discontinued if markedly elevated CPK levels occur or if myopathy is diagnosed or suspected. *Pregnancy:* Contra-indicated. One month should elapse between ending therapy with 'Zocor' and planned conception. *Drug interactions:* Care should be taken in patients on concomitant lipid-lowering therapy, particularly fibrates or nicotinic acid derivatives or immunosuppressive therapies.

4-91 ZCR.89.GB.4162.J

BRITAIN
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HEART

A BREAKTHROUGH IN CHOLESTEROL CONTROL HAS ARRIVED

The link between coronary heart disease and elevated cholesterol is strong and consistent.[1] The UK has one of the worst records for coronary heart disease in the world. If we are to improve our record we must strive to improve all of our nation's risk factors, including cholesterol. It has been estimated from a study of hypercholesterolaemic men that a 1% reduction in cholesterol reduces the risk of coronary heart disease by 2%.[2]

Zocor® (simvastatin, MSD), the first available HMG-CoA reductase inhibitor, is a major breakthrough in cholesterol control from Merck Sharp & Dohme. 'Zocor' is indicated for use in patients with primary hypercholesterolaemia, intolerant or not responsive to other forms of therapy, and who have cholesterol levels in excess of 7.8 mmol/l.

'Zocor' achieves up to 32% reduction of total cholesterol,[3] a reduction unsurpassed by any existing agent. In conjunction with a cholesterol-lowering diet, 'Zocor' is generally well accepted by patients[3] and, in contrast to the majority of agents, is available as a once-daily tablet.

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(simvastatin, MSD)

Reducing cholesterol to help reduce coronary risk

IDE EFFECTS
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. Study Group, *Europ. Heart J.*, 1987, **8**, 77.
. Lipid Research Clinics Programme, *J. Amer. med. Ass.*, 1984, **251**, 351-364.
. Data on file, Merck Sharp & Dohme Limited.

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Editorial

Ultrasound and coarctation of the aorta

Initial reports of cross sectional echocardiography in the diagnosis of coarctation of the aorta were very promising,[1 2] with the technique allowing operation to be carried out without invasive investigation in many patients.[3] As experience grew, however, it became clear that high quality images of the aortic arch are not universally obtainable, that cross sectional echocardiography does not always provide an answer, and that occasionally it may even lead to false positive diagnosis of an aortic arch obstruction.[4] Doppler ultrasound was welcomed as a solution. Published studies were reassuring; calculation of the pressure drop across the site of coarctation by the modified Bernoulli equation was reported to reflect accurately both the blood pressure difference between the upper and lower limbs[5 6] and the invasively measured pressure gradient,[7–9] but again experience proved this approach to be too simplistic. Just as for other cardiovascular stenoses, gradients estimated by Doppler represent maximum instantaneous values rather than the traditionally used difference between peak systolic pressures on both sides of an obstruction. The differences between these two measurements may be considerable and clinically important.[10]

Disappointingly, even when these differences are taken into account, in some patients there is poor agreement between the coarctation gradients measured invasively and by Doppler.[11 12] Various factors are responsible for this. It can be difficult to align the Doppler beam with flow, complex flow dynamics in the aortic arch may invalidate some of the assumptions made in the calculation of pressure drop, and a tunnel like stenosis when present is a less suitable subject for Doppler calculations than a discrete obstruction.[13] Furthermore, it is now clear that severe obstruction of the aortic arch may be associated with normal or near normal aortic flow velocities depending on the state of the ductus arteriosus[12 14] or the presence of extensive collaterals.[15]

Use of the pressure gradient as an indicator of severity of valve stenosis has long been recognised as being fraught with problems, largely related to the dependence of gradient on blood flow. Similar confusion about the value of the pressure gradient in coarctation is understandable because this too is dependent on factors other than the degree of obstruction. Stroke volume, the presence of a ductus arteriosus, and the extent of the collateral supply to the descending aorta are all important factors. Thus many of the difficulties associated with the assessment of the severity of valve stenosis[16] are common to the assessment of coarctation and could be avoided, at least in theory, if the effective orifice area at the site of the coarctation could be estimated.

The concept of pressure decay (a square function of velocity decay) across an obstruction to flow as an indicator of effective orifice area has long been applied to fluid dynamics and was first applied in invasive cardiology to mitral stenosis,[17] later being adapted for use with Doppler ultrasound.[18] Disappointingly, like most single variables in heart disease, pressure decay across the mitral valve is affected by factors other than stenosis—such as ventricular compliance and aortic regurgitation.

Dr Carvalho and her colleagues (p 133) confirmed that the Doppler pressure drop alone cannot always be relied upon to predict the severity of coarctation of the aorta. They propose an additional measurement of diastolic flow velocity decay—the time to half peak diastolic velocity. This is defined as the time taken for flow velocity to fall from its peak value in diastole (measured at the end of the T wave of the electrocardiogram) to half this value. Prolonged flow deceleration in coarctation has long been recognised as diagnostically important[6 19–21] but little effort has been made to introduce a simple quantitative measurement of it, such as the time to half peak diastolic velocity. The combination of this measurement with peak systolic velocity considerably improved both the test sensitivity and the predictive value of a negative test compared with either measurement used alone in the patients studied.

There seems little doubt that pressure (or velocity) decay across the aortic arch in coarctation will also be affected by factors such as vascular resistance, the competence of the aortic valve, the presence of a ductus arteriosus, and the extent of collateral blood supply to the descending aorta. In the absence of these complicating factors, the combination of measurements of peak flow velocity and flow velocity decay is clearly useful. However, when complicating factors are present uncertainty will still arise, and then the best reference standard is still probably angiographic measurement of the aortic lumen as used by Carvalho *et al*. Even angiography may be difficult to interpret, however, because it is dependent on arbitrarily defined criteria of severity mainly relating to anatomical features. The importance of careful consideration of physiology as well as anatomy was emphasised by studies during exercise after operation for coarctation. Some alarming physiological changes may be seen with exercise even when there are no striking signs of residual or recurrent coarctation at rest.[22–25]

Non-invasive assessment of the severity of coarctation may be enhanced by measurement of velocity decay as well as peak flow velocity, but even the combination of these two measurements will not provide an answer in every patient. Further improvement in diagnosis is clearly desirable and it is hoped will prove possible with continued attempts to develop a combined anatomical and physiological approach that should involve exercising the patient.

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1 Huhta JC, Gutgesell JP, Latson LA, Huffines FD. Two dimensional echocardiographic assessment of the aorta in infants and children with congenital heart disease. *Circulation* 1984;**70**:417–24.

2 Smallhorn JF, Huhta JC, Adams PA, Anderson RH, Wilkinson JL, Macartney FJ. Cross-sectional echocardiographic assessment of coarctation in the sick neonate and infant. *Br Heart J* 1983;**50**:349–61.

3 Duncan WJ, Ninomiya K, Cook DH, Rowe RD. Noninvasive diagnosis of neonatal coarctation and associated anomalies using two-dimensional echocardiography. *Am Heart J* 1983;**106**:63–9.

4 Nihoyannopoulos P, Karas S, Sapsford RN, Hallidie-Smith K, Foale R. Accuracy of two-dimensional echocardiography in the diagnosis of aortic arch obstruction. *J Am Coll Cardiol* 1987;**10**:1072–7.

5 Wyse RKH, Robinson PJ, Deanfield JE, Tunstall Pedoe DS, Macartney FJ. Use of continuous wave Doppler ultrasound velocimetry to assess the severity of coarctation of the aorta by measurement of aortic flow velocities. *Br Heart J* 1984;**52**:278–83.

6 Barth H, Hassberg D, Schmalz AA, Steil I, Apitz J. Continuous-wave Doppler velocimetry and blood pressure difference in coarctation of the aorta—a simultaneous correlative study in 52 children. *Herz* 1987;**12**: 217–25.

7 Robinson PJ, Wyse RKH, Deanfield JE, Franklin R, Macartney FJ. Continuous wave Doppler velocimetry as an adjunct to cross sectional echocardiography in the diagnosis of critical left heart obstruction in neonates. *Br Heart J* 1984;**52**:552–6.

8 Hoadley SD, Duster MC, Miller JF, Murgo JP. Pulsed Doppler study of coarctation of the aorta: demonstration of a continuous Doppler frequency shift. *Pediatr Cardiol* 1986;**6**:275–7.

9 Marx GR, Allen HD. Accuracy and pitfalls of Doppler evaluation of the pressure gradient in aortic coarctation. *J Am Coll Cardiol* 1986;7: 1379–85.

10 Currie PJ, Hagler DJ, Seward JB, *et al.* Instantaneous pressure gradient: a simultaneous Doppler and dual catheter correlative study. *J Am Coll Cardiol* 1986;7:800–6.

11 Stevenson JG, French JW, Kawabori I. Doppler measurement of coarctation gradients [Abstract]. *Circulation* 1985;72 (part II):III–5.

12 Houston AB, Simpson IA, Pollock JCS, Jamieson MPG, Doig WB, Coleman EN. Doppler ultrasound in the assessment of severity of coarctation of the aorta and interruption of the aortic arch. *Br Heart J* 1987;**57**:38–43.

13 Teirstein PS, Yock PG, Popp RL. The accuracy of Doppler ultrasound measurement of pressure gradients across irregular, dual, and tunnellike obstructions to blood flow. *Circulation* 1985;**72**:577–84.

14 Wilson N, Sutherland GR, Gibbs JL, Dickinson DF, Keeton B. Limitations of Doppler ultrasound in the diagnosis of neonatal coarctation of the aorta. *Int J Cardiol* 1989;**23**:87–9.

15 Scott PJ, Wharton GA, Gibbs JL. Failure of Doppler ultrasound to detect coarctation of the aorta. *Int J Cardiol* 1990 (in press).

16 Odemuyiwa O, Hall RJC. Assessing the severity of valve stenosis. *Br Heart J* 1986;**55**:117–9.

17 Libanoff AJ, Rodbard S. Atrioventricular pressure half time. Measure of mitral valve orifice area. *Circulation* 1968;**38**:144–50.

18 Hatle L, Angelsen B, Tromsdal A. Noninvasive assessment of atrioventricular pressure half-time by Doppler ultrasound. *Circulation* 1979; **60**:1096–104.

19 Hagler DJ, Tajik AJ, Seward JB, Ritter DG. Noninvasive assessment of pulmonary valve stenosis, aortic valve stenosis and coarctation of the aorta in critically ill neonates. *Am J Cardiol* 1986;**57**:369–72.

20 Shaddy RE, Snider AR, Silverman NH, Lutin W. Pulsed Doppler findings in patients with coarctation of the aorta. *Circulation* 1986;**73**:82–8.

21 Rao PS, Carey P. Doppler ultrasound in the prediction of pressure gradients across aortic coarctation. *Am Heart J* 1989;**118**:299–307.

22 Earley A, Joseph MC, Shinebourne EA, de Swiet M. Blood pressure and effect of exercise in children before and after surgical correction of coarctation of aorta. *Br Heart J* 1980;**44**:411–5.

23 Freed MD, Rocchini A, Rosenthal A, Nadas AS, Castaneda AR. Exercise-induced hypertension after surgical repair of coarctation of aorta. *Am J Cardiol* 1979;**43**:253–8.

24 Waldman JD, Goodman AH, Tumeo AR, Lamberti JJ, Turner SW. Coarctation of aorta. Noninvasive physiological assessment in infants and children before and after operation. *J Thorac Cardiovasc Surg* 1980;**80**:187–97.

25 Waldman JD, Lamberti JJ, Goodman AH, *et al.* Coarctation in the first year of life. Patterns of postoperative effect. *J Thorac Cardiovasc Surg* 1983; **86**:9–17.

Br Heart J 1990;**64**:111-2

Editorial

ST segment changes as a surrogate end point in coronary thrombolysis

The role of thrombolysis in the treatment of acute myocardial infarction is now established by the GISSI study, which was presented at the time of the American College of Cardiology scientific sessions in New Orleans in March 1990. The enormous size and costs required to measure the difference in mortality in comparative trials impose many limitations and in future small specific subsets will need to be studied. There is increasing interest in examining surrogate end points for coronary artery patency in such studies.

The extent of the improvement in left ventricular function shown after reperfusion is disproportionately small compared with the associated reduction in mortality, suggesting that reperfusion has an as yet unidentified benefit. The patency of the infarct related vessel therefore remains the main goal of treatment and coronary arteriography remains the "gold standard" for the assessment of reperfusion. Identification of reperfusion is important in the assessment of the efficacy of new thrombolytic agents, differing regimens of administration of available agents (such as bolus dosing), or the role of adjunctive medication such as antiplatelet treatment. The identification of arteries that remain occluded is also important because it predicts a higher mortality in some patients, who might benefit from early additional intervention such as intracoronary thrombolysis or salvage angioplasty.

The complications associated with early angiography have been overestimated because they may include those of angioplasty with its additional risk of bleeding complications and coronary artery occlusion. Further assessment of the risk-benefit ratio of angiography in acute myocardial infarction is required, because the management of patients may be improved by the identification of the number of diseased vessels, the patency or occlusion of the infarct related artery, and early assessment of left ventricular function. A recent trial to compare the angiographically demonstrated patency rates achieved after the administration of either anistreplase or streptokinase focused attention on the ethical aspects of performing invasive procedures early after myocardial infarction in the presence of thrombolysis.[1,2] We need to know more about the risks of local haemorrhage, bleeding at distant sites, and the morbidity associated with angiography.

Non-invasive assessment of reperfusion

Non-invasive markers associated with reperfusion have been tested to determine their specificity and sensitivity in predicting early vessel patency. Reperfusion may alter the temporal patterns of release of creatine kinase or its specific cardiac isoenzyme. Myoglobin or myosin release may show different temporal and qualitative patterns with reperfusion. Because these investigations are not immediately available in most coronary care units, such determinations tend to be retrospective, which limits their clinical usefulness for decisions made early in the course of myocardial infarction.

The measurement of the changes in the ST segment of the electrocardiogram therefore remains an attractive non-invasive investigation. It is widely used and understood and can be repeated with a high degree of reproducibility. Group studies showed that there is a greater fall in ST segment elevation in patients who reperfuse than in those who do not. We still do not know how useful this measurement is in predicting reperfusion in individual patients. The use of various methods to analyse the changes in ST segment – measurements from multiple dipole electrograms, the sum of ST segments over a 12 lead electrocardiogram, or serial assessment of individual leads showing significant ST elevation – has led to confusion. The assessment of the degree of ST segment change (expressed as a percentage fall or as a fractional change) that can be considered diagnostic, the timing of the reference electrocardiogram, and other clinical variables are also important. Clinical factors include the time from the onset of symptoms, the presence of previous myocardial infarction, and the influence of collateral vessels (which may affect myocardial perfusion if the culprit artery is occluded).

In our recent comparative study, the coronary artery patency achieved after anistreplase increased from 55% on first visualisation to 64% at the end of angiography performed 90 minutes after administration. This emphasises that the findings in the early period after thrombolysis are very variable and that the electrocardiographic criteria to indicate reperfusion will only be valid if applied to electrocardiograms recorded at the appropriate time. Previous studies suggested that a fractional change of 50% was highly specific and sensitive for determining coronary artery patency.[3] This study was limited by the small number of patients who did not achieve reperfusion. Angiography was performed relatively late which may have led to a falsely high patency rate.

Saran *et al* (page 113) examined the specificity and sensitivity of a fractional change to 25% for predicting coronary artery patency; they also assessed its relation to left ventricular function. They used careful angiographic studies with TIMI grade classification and non-invasive and invasive assessments of left ventricular function. They did not study many patients, however, and the high degree of patency achieved by thrombolysis or by the addition of angioplasty meant that only eight of the series of 45 had non-patent arteries. In addition, three of the patients had well developed collateral vessels, and this may have influenced the subsequent improvement in the ST segment. None the less, the concept that failure to reduce the ST segment by 25% over 3 hours can predict non-reperfusion is an attractive one. Melandri *et al* (page 118) presumed that a reduction in ST segment elevation predicted reperfusion and they used the time to a reduction in fractional change of 50% to assess the results of two treatments – streptokinase alone and streptokinase with heparin. The electrocardiograms were taken at the same time as the measurements used to construct concentration curves for serum creatine kinase. This small study suggests that differences associated with different thrombolytic regimens can be identified.

The two studies in the current issue continue the debate on the usefulness of ST segment changes as surrogate end points for reperfusion. Coronary angiography remains the reference standard, and the ethics of performing early angiography need further discussion. We believe that angiography is justifiable if the patient can give informed consent and the issues are discussed with any accompanying relatives. Prospective studies are needed of patients who show no fall in ST segment elevation 3 hours after thrombolysis. Early angiography and intervention, either by intracoronary thrombolysis or angioplasty, need to be evaluated in this group. Further studies are also required of electrocardiographic and biochemical markers to improve the non-invasive identification of coronary artery reperfusion.

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1 Hogg KJ, Gemmill JD, Burns JMA, *et al.* Angiographic patency study of anistreplase versus streptokinase in acute myocardial infarction. *Lancet* 1990;**335**:254–8.
2 Anonymous. Surrogate measures in clinical trials. *Lancet* 1990;**335**:261–2.
3 Hogg KJ, Hornung RS, Howie CA, Hockings N, Dunn FG, Hillis WS. Electrocardiographic prediction of coronary artery patency after thrombolytic treatment in acute myocardial infarction; use of the ST segment as a non-invasive marker. *Br Heart J* 1988;**60**:275–80.

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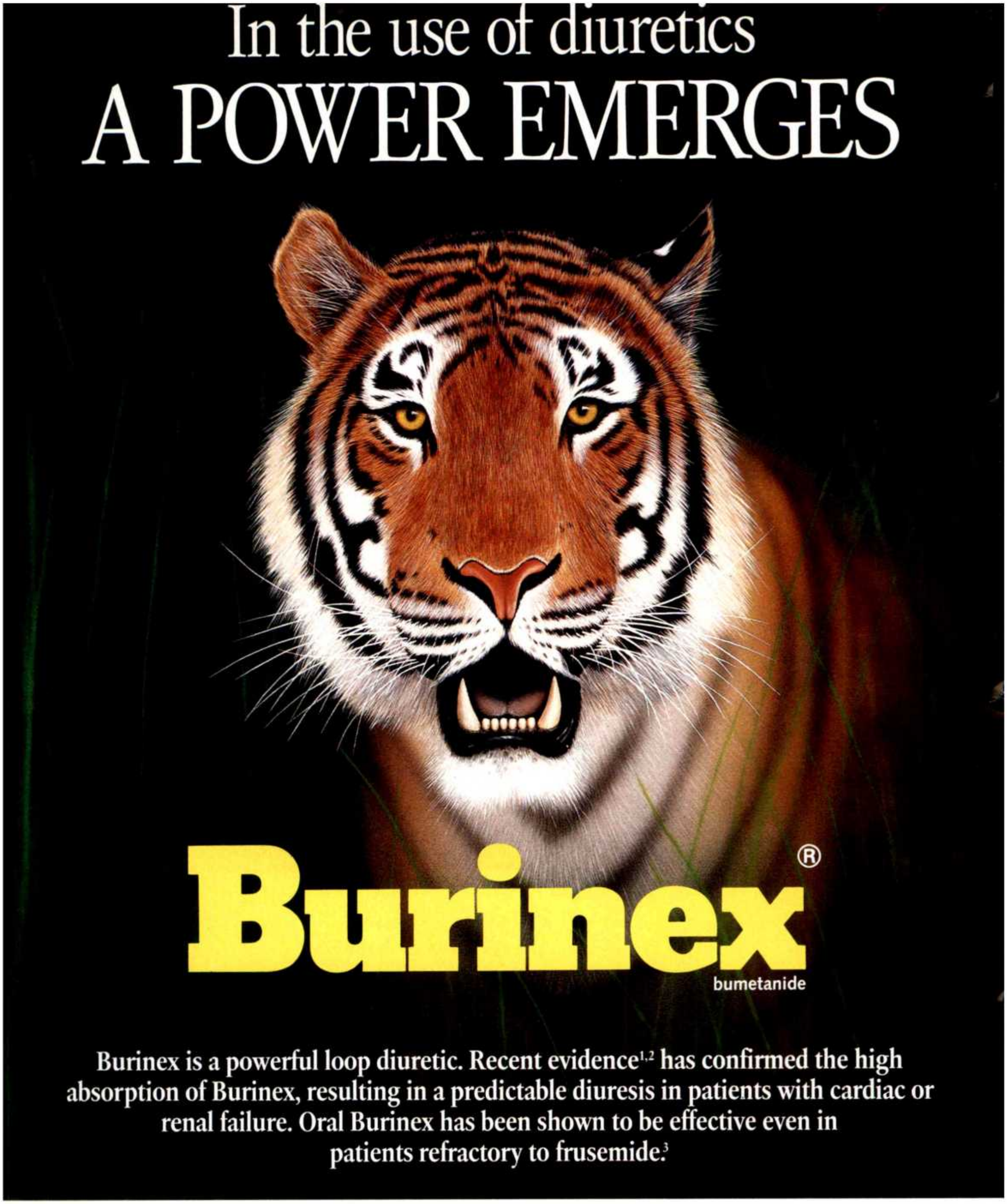

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References
1. Cook, J.A. et al., Clin. Pharmacol. Ther., **44**, 487, 1988.
2. Lau, H.S.H. et al., Clin. Pharmacol. Ther., **39**, 635, 1986.
3. Pines, A. et al., Br. J. Clin. Pract., **28(9)**, 311, 1974.

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ORIGINAL ARTICLES

Reduction in ST segment elevation after thrombolysis predicts either coronary reperfusion or preservation of left ventricular function

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Abstract

The usefulness of a reduction in ST segment elevation to predict coronary reperfusion in myocardial infarction remains uncertain. ST segment changes and angiographic findings were compared in 45 patients soon after thrombolysis. The percentage ST segment change 3 hours after treatment (in the lead showing the greatest initial ST elevation) was compared with the TIMI perfusion grade (thrombolysis in myocardial infarction trial) obtained between 90 minutes and 3 hours after treatment. Global ejection fraction and regional wall motion were assessed by cineventriculography (11 (5) days (mean (SD))) and by gated blood pool imaging (44 (11) days). Prediction of coronary patency by a reduction of >25% in ST segment elevation 3 hours after thrombolytic treatment had a sensitivity of 97% but a specificity of only 43%. Where the ST segment elevation was reduced by >25% the global ejection fraction was well maintained whether or not the infarct vessel was patent. In patients with a reduction of <25% in ST elevation, the ejection fraction was significantly lower and regional wall motion abnormality more severe.

Reduction in ST elevation of >25% within 3 hours of thrombolysis indicates either a patent infarct artery or preservation of left ventricular function. When the ST segment elevation does not fall by >25% persistent coronary occlusion is likely (predictive accuracy 86%) and is associated with a lower ejection fraction. These patients may benefit from further treatment or additional interventions.

Treatment by intravenous thrombolysis in acute myocardial infarction reduces mortality,[1] preserves left ventricular function,[2] and is now widely accepted. Non-invasive detection of reperfusion may be a useful guide to future treatment. Mortality is higher in patients in whom thrombolysis does not lead to reperfusion[3 4] and such patients may benefit from early additional interventions such as salvage angioplasty. A rapid reduction in ST segment elevation,[5] relief from chest pain,[6] early peaking of serum concentrations of creatine kinase,[7] and reperfusion arrhythmias[8] are some of the markers used to predict reperfusion non-invasively. In a review of electrocardiographic studies after thrombolysis Bren *et al* concluded that when large groups are analysed, the magnitude of the reduction in ST elevation is greater in groups with reperfusion than in those without or in a control group.[9] They suggested, however, that in individual patients reduction in ST segment elevation is of limited value in predicting reperfusion and left ventricular function. On the other hand, Hogg *et al* reported that the 12 lead electrocardiogram is a simple and useful method for determining reperfusion in individuals.[10] We therefore studied the usefulness of early changes in the ST segment in predicting vessel patency and preservation of left ventricular function after thrombolysis.

Patients and methods

This study was part of a randomised trial to investigate the effects of percutaneous transluminal coronary angioplasty immediately after thrombolytic treatment. Forty five consecutive patients with acute infarction who fulfilled the entry criteria for the above study were given intravenous anisoylated streptokinase plasminogen activator complex (anistreplase) between August 1987 and November 1988. The criteria for inclusion into the study were: (*a*) ischaemic chest pain lasting >30 minutes but <4 hours; (*b*) ST segment elevation of at least 0·2 mV in two or more precordial leads or 0·1 mV in two or more standard limb leads; (*c*) aged ⩽70; (*d*) gave consent to the study; (*e*) no contraindication to thrombolytic treatment or angiography.

A pretreatment 12 lead electrocardiogram was recorded and the sites of leads V1 to V6 were marked on the chest to ensure consistent electrode placement for subsequent electrocardiograms. All patients were given 30 units of anistreplase by intravenous injection over 5 minutes. Coronary angiography was performed at 60 minutes and at 90 minutes after treatment with anistreplase. Patients randomly allocated to percutaneous transluminal coronary angioplasty underwent balloon dilatation of the culprit lesion immediately after the 90 minute angiogram

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unless there was a left main stem lesion or the stenosis in the infarct artery was less than 50%. Vessel patency was assessed 15 minutes after the last balloon inflation. The arterial sheath was left in position and heparin was infused at a rate of 1000 units per hour.

A repeat electrocardiogram was recorded at 3 hours after anistreplase treatment (mean (SD) 206 (35) minutes). Repeat coronary angiography was performed at 24 hours after which the sheath was removed.

ELECTROCARDIOGRAPHIC ANALYSIS

Electrocardiograms recorded before thrombolysis and 3 hours afterwards were analysed by an observer who was unaware of the angiographic findings or clinical details. The lead showing the greatest ST segment elevation at presentation was used for subsequent measurement of ST segments. We used callipers to measure ST elevation and we took the mean of three complexes. The isoelectric line was defined as the level of the preceding TP segment and ST segment elevation was measured at the J point. The mean change in ST segment elevation after thrombolytic treatment was expressed as a percentage reduction or increase from the initial value.

CORONARY ANGIOGRAPHIC ANALYSIS

The coronary angiograms were analysed by two observers who were unaware of the electrocardiographic results. Coronary perfusion was assessed by the TIMI (thrombolysis in myocardial infarction trial) criteria.[11] TIMI grades 0 and 1 were classified as non-patent arteries and TIMI grades 2 and 3 as a patent artery. The collateral circulation was also evaluated on a scale of 0 to 3.[12] The collateral score was based on the injection that best opacified the occluded vessel. In grade 0 there was no filling, in grade 1 filling of side branches of the occluded vessel could be seen, while in grade 2 there was partial filling of the epicardial segment, and in grade 3 there was complete filling of the epicardial segment of the occluded vessel via collaterals.

LEFT VENTRICULAR FUNCTION

Left ventricular function was evaluated from biplane contrast cineventriculograms before hospital discharge at 11 (5) days and by gated blood pool imaging (technetium-99m labelled pyrophosphate) at 44 (14) days.

Contrast ventriculography was performed in 39 patients. It was not performed in patients who refused consent (n = 1), who had coronary bypass grafting (n = 1) or percutaneous transluminal angioplasty outside the protocol (n = 1), or who were considered too ill (n = 1) for the procedure. Practical reasons prevented two more patients from having contrast ventriculography. The ejection fraction was calculated from tracings taken by projecting the right anterior oblique view but four patients were excluded from analysis of global left ventricular function because of a previous myocardial infarction. We assessed regional wall motion by dividing the left anterior oblique projection into three segments (septal (1), inferoapical (2), posterolateral (3)) and the right anterior oblique into five segments (high anterior (4), low anterior (5), apical (6), inferior (7), and posterior (8)). Segments with normal motion were scored as zero whereas hypokinesia, akinesia, and dyskinesia were scored as 1, 2, or 3 respectively—so the lower the total score in the infarct territory the better the preservation of left ventricular function. To exclude the influence of prior myocardial infarction on the results we scored only those segments associated with the infarct related artery. The wall motion score was calculated from segments 1, 4, 5, and 6 in anterior infarction and from segments 2, 3, 7, and 8 in inferior infarction.

The gated blood pool study was performed in 44 patients (one patient refused and in one patient the image quality was too poor for analysis). The global left ventricular ejection fraction was calculated by a semi-automated double region method for the left anterior oblique view. The four patients with previous myocardial infarction were also excluded from this analysis.

The regional wall motion abnormality score was assessed by dividing the left anterior oblique projection into three segments and the left lateral projection into five segments and wall motion scores were graded as for the contrast ventriculograms.

STATISTICAL ANALYSIS

We calculated the sensitivity and specificity of a reduction in ST elevation of >25% and >50% for perfusion and for no reperfusion. Statistical significance was determined by a two-sample analysis of variance. A p value of $<0\cdot05$ was regarded as significant.

Results

The mean age of the patients was 55 years (range 30–69). Forty two were men. Twenty five had an anterior infarction and 20 an inferior infarction. The mean interval from onset of chest pain to anistreplase treatment was 153 minutes (range 50 to 240). Table 1 shows the age, culprit artery, time from onset of symptoms to anistreplase administration, previous myocardial infarction if any, percentage reduction in ST elevation at 3 hours, TIMI grading at 90 minutes and 24 hours, and global ejection fraction in each of the 45 patients.

In 31 of the 45 patients the culprit coronary artery was patent 90 minutes after anistreplase or after percutaneous transluminal coronary angioplasty. All but one of these 31 patients showed a reduction in ST segment elevation by >25% at 3 hours (table 2). Thus our results show that reduction in ST segment elevation of >25% had sensitivity of 97% in predicting coronary patency. This compares with a sensitivity of 68% when we used the criterion of a reduction of >50%. ST segment elevation was reduced by >25% in eight of 14 patients with a persistently occluded infarct related artery, indicating a specificity of only 43% for determining patency by this criterion.

Table 1 Individual patient details, reduction in ST elevation at 3 hours, TIMI perfusion grade, and global ejection fraction at 6 weeks

Patient No	Age (yr)	Infarct vessel	Prior MI	Symptom duration (min)	ST reduction (%)	TIMI grade at: 90 min	24 h	Global EF (%)
1	46	LAD	—	200	66	3	3	54
2	62	RCA	—	92	66	3	3	63
3	51	LAD	—	64	52	2	0	40
4	45	RCA	—	180	80	2	3	30
5	42	RCA	—	130	50	3	1	—
6	62	RCA	—	89	66	3	3	48
7	63	LAD	—	118	80	0	0	51
8	53	LAD	—	150	33	3	3	62
9	47	LAD	—	149	55	2	3	48
10	63	Cx	—	230	100	3	3	58
11	47	Cx	+	85	75	2	3	52
12	48	LAD	—	175	75	2	3	26
13	66	LAD	—	155	65	2	3	34
14	57	RCA	+	137	68	0	0	29
15	57	LAD	—	95	69	3	3	45
16	65	LAD	—	52	50	2	–	27
17	65	RCA	—	150	42	3	3	57
18	58	RCA	+	135	100	0	0	54
19	56	LAD	—	192	37	2	2	21
20	44	RCA	—	229	38	0	2	28
21	47	Cx	—	240	75	2	3	33
22	69	LAD	—	220	−60	0	0	6
23	45	LAD	—	110	80	2	3	28
24	68	LAD	+	185	30	3	2	39
25	53	LAD	—	210	73	3	1	52
26	30	LAD	—	101	36	3	3	52
27	48	RCA	—	150	7	1	2	42
28	59	LAD	—	218	−42	1	2	33
29	61	LAD	—	240	52	2	0	53
30	46	LAD	—	195	6	0	0	45
31	62	LAD	—	195	−70	0	–	20
32	48	RCA	—	70	66	3	3	61
33	58	LAD	—	225	75	1	3	36
34	66	Cx	—	223	75	3	3	*
35	55	LAD	—	115	66	1	3	59
36	59	RCA	—	88	56	3	3	60
37	63	RCA	—	110	87	3	3	38
38	64	LAD	—	190	66	3	3	57
39	55	LAD	—	140	−200	3	3	26
40	48	RCA	—	92	33	3	3	50
41	59	LAD	—	175	55	0	3	51
42	55	Cx	—	158	66	3	3	68
43	49	RCA	—	193	83	0	2	48
44	61	RCA	—	132	30	2	0	45
45	65	LAD	—	50	−300	1	0	20

*Technically poor image, LAD, left anterior descending artery; RCA, right coronary artery; Cx, circumflex artery, MI, myocardial infarction, EF, ejection fraction

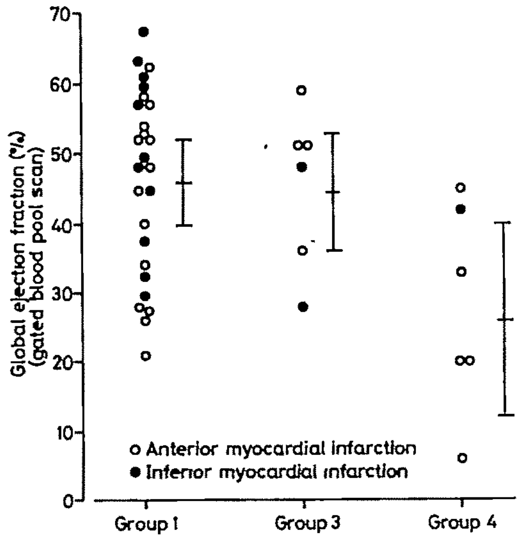
Table 2 Percentage reduction or increase in ST segment elevation at 3 hours in patients with and without coronary perfusion

Coronary patency (TIMI grade)	Percentage reduction in ST segment elevation: >50%	25–50%	<25%	increase
0–1	7	1	2	4
2–3	21	9	0	1

In five patients the ST segment elevation increased further and in two patients the reduction in ST segment elevation was <25%. In all but one of these patients the infarct related artery was occluded. The absence of a reduction of >25% in ST segment elevation 3 hours after thrombolysis is highly specific (97%) for coronary occlusion.

The perfusion and electrocardiographic data were used to divide the patients into four groups. Group 1 (n = 30) comprised patients with a patent artery and a reduction of >25% in ST elevation while group 2 (n = 1) was a patient with a patent artery and a reduction of <25%. Group 3 (n = 8) included those with a non-perfusing artery but a reduction of >25% in ST elevation while group 4 (n = 6) comprised those with an occluded artery and a reduction of <25% in ST segment elevation.

Group 2 was excluded from analysis because it contained only one patient. The figure shows a comparison of the global left ventricular ejection fraction measured by gated blood pool imaging in the remaining groups. The ejection fraction (mean (SD)) was highest in those with patent vessels (47 (13)%) (group 1). This was



Left ventricular ejection fraction in patients with ≥ 25% reduction in ST elevation (group 1 = patent, group 3 = occluded) and in patients with <25% reduction in ST segment elevation and occluded arteries (group 4).

Table 3 Global ejection fraction and mean regional wall motion abnormality score in the different groups (mean (SD))

		Ventriculogram (n = 39)		*Gated blood pool scan (n = 43)*	
Group	*Symptom duration (min)*	*Ejection fraction*	*Wall motion score**	*Ejection fraction*	*Wall motion score**
1	145 (56)	55 (14)	2·7 (2)	47 (13)	2·5 (2)
3	166 (46)	57 (25)	3·0 (2)	46 (11)	2·4 (3·1)
4	171 (65)	40 (9)	4·8 (1)	28 (15)	4·7 (3·2)

*Mean regional wall motion score of infarct related segments.
Group 1—patent artery and ≥25% reduction in ST elevation.
Group 3—non-perfusing artery but ≥25% reduction in ST elevation.
Group 4—occluded artery and <25% reduction in ST segment elevation.

similar to group 3 where the ejection fraction was 46 (11)%. Group 4 had a significantly lower ($p < 0{\cdot}05$) ejection fraction (28 (15)%). A similar trend was seen with the ejection fraction measured by cineventriculography (table 3). The duration of symptoms before thrombolysis was not significantly different in the three groups.

The mean regional wall motion abnormality score measured on the contrast left ventricular angiogram was 2·7 in group 1, 3·0 in group 3, and 4·8 in group 4 (not statistically significant). A similar trend was seen with mean regional wall motion score obtained by gated blood pool imaging.

Three of the eight patients in group 3 (occluded vessels and reduction in ST elevation (>25%)) had well developed collateral flow to the infarct related artery (collateral grade 2 and 3). These three patients had inferior wall infarction and there was complete filling of the posterior descending artery via collaterals. In four of the remaining five patients in group 3 there was reperfusion between 90 minutes and 24 hours after thrombolysis.

Two of the six patients in group 4 had poorly developed collaterals (grade 1) and no collateral flow was seen in the remaining four patients. In two of the patients in group 4 there was reperfusion between 90 minutes and 24 hours.

Discussion

Simple and rapid methods for determining perfusion state are required if decisions about additional treatment or procedures need to be made early after thrombolysis. Prediction from creatine kinase curves and from most Holter monitoring systems will only allow a retrospective diagnosis of reperfusion. It has been suggested that analysis of the ST segment by single or multiple electrocardiographic leads is useful but there is no consensus about the degree of reduction in ST segment elevation needed to predict reperfusion because different techniques and criteria have been used. The lead showing the greatest ST segment elevation was selected in this study primarily for simplicity so that a useful clinical tool might be defined, but also to allow comparison with many other studies. In addition it is highly likely that this lead would follow the same course both in time and magnitude as the sum of ST changes in all leads.

We found that an early reduction of ST segment elevation by >25% after thrombolytic treatment for acute myocardial infarction is highly sensitive for coronary perfusion (97%) but has poor specificity (43%). Hogg *et al* reported a high sensitivity (93%) for a fall of >50% in the lead showing maximum ST elevation, with a specificity of 67%.[10] There was, however, a wide variation in the mean (SD) time of the post-thrombolytic electrocardiogram (302 (141) minutes) in their study and perfusion criteria were not given. When we used a 50% reduction in ST elevation there was a fall in sensitivity to 68% and a slight improvement in specificity (50%). Richardson *et al* reported a specificity of 67% but with a poor sensitivity (26%) when a single lead showing the maximal ST segment elevation was used to predict coronary artery patency.[13] They used a reduction of 2 mm in ST segment elevation or normalisation of the ST segment as the criteria for patency, and confirmation of angiographic patency was only performed at a mean of 6 days after thrombolytic treatment. The likelihood of spontaneous or late reperfusion in many of these patients seriously hampers the usefulness of Richardson *et al*'s study in determining the accuracy of an early reduction in ST segment elevation in predicting early coronary perfusion.

Our study suggests that an early reduction in ST segment elevation is of limited value in predicting the patency of the coronary artery in an individual patient (low specificity). Perhaps more importantly the study shows that failure of ST segment elevation to be reduced by >25% indicates persisting coronary occlusion. Von Essen *et al* also reported a persistence of or an increase in ST segment elevation in leads I, II, and III in nine out of 10 patients with unsuccessful thrombolysis.[14] There remains, however, a separate group (group 3) with persistent occlusion in whom the ST segment falls to the same extent as in reperfusion. The ejection fraction and regional wall motion score in this group resembled values in the group with coronary perfusion. The TIMI group also reported a significant correlation ($p < 0{\cdot}01$; $r = 0{\cdot}43$) between the decline in ST elevation two hours after thrombolytic treatment and the residual left ventricular ejection fraction at discharge.[15] The reason for the fall in the ST segment in the absence of reperfusion is unclear in these patients. It is unlikely that the ST segment fell in these patients because of more rapid death of myocardial cells because this would have resulted in a lower ejection fraction and higher score for regional wall motion abnormality.

In three (of eight patients in our study) the reduction in ST elevation was probably due to the presence of collaterals and in four (of the remaining five) it is possible that reperfusion occurred between 90 minutes and three hours because the infarct vessel was patent at 24 hours. This still leaves one patient in whom there were no collaterals and the infarct artery was still occluded at 24 hours.

We chose to assess the 12 lead electrocardiogram three hours after thrombolytic treatment but it may be that even earlier assessment would be of value. Von Essen *et al* showed that where there is a reduction in ST elevation much of this occurs within one hour of reperfusion.[14]

Whatever the explanation for the reduction in ST elevation our results suggest that a fall of $>25\%$ in the lead showing maximal initial ST elevation within three hours of thrombolysis is indicative of either a patent infarct related coronary artery or preservation of left ventricular function despite coronary occlusion.

Thus reduction in ST elevation seems to select out a group of patients likely to have a good outcome. The remaining patients who do not show a fall in ST elevation of $>25\%$ have both persistent coronary occlusion (specificity 97%) and a lower ejection fraction and so may benefit from further treatment or acute interventions.

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1 ISIS-2 (Second international study of infarct survival) Collaborative group. Randomised trial of intravenous streptokinase, oral aspirin, both, or neither among 17 187 cases of suspected acute myocardial infarction· ISIS-2. *Lancet* 1988;ii:349–60.
2 White HD, Norris RM, Brown MA, *et al*. Effect of intravenous streptokinase on left ventricular function and early survival after acute myocardial infarction. *N Engl J Med* 1987;317:850–5.
3 Been M, Muir AL, de Bono DP. Left ventricular function after anisoylated plasminogen streptokinase activator complex. *Drugs* 1987;33(suppl 3)·191–7.
4 Kennedy JW, Martin GV, Davis KB, *et al*. The Western Washington intravenous streptokinase in acute myocardial infarction randomized trial. *Circulation* 1988; 77:345–52
5 Krucoff MW, Green CE, Satler LF, *et al*. Noninvasive detection of coronary artery patency using continuous ST-segment monitoring. *Am J Cardiol* 1986,57.916–22
6 Lee G, Amsterdam EA, Low R, *et al*. Efficacy of percutaneous transluminal coronary recanalization utilizing streptokinase thrombolysis in patients with acute myocardial infarction. *Am Heart J* 1981;102:1159–67.
7 Been M, de Bono DP, Muir AL, Boulton FE, Hillis WS, Hornung R Coronary thrombolysis with intravenous anisoylated plasminogen-streptokinase complex BRL 26921 *Br Heart J* 1985;53·253–9.
8 Rutsch W, Schartl M, Mathey D, *et al*. Percutaneous transluminal coronary recanalisation procedure, results, and acute complications. *Am Heart J* 1981;102:1178–81.
9 Bren GB, Wasserman AG, Ross AM. The electrocardiogram in patients undergoing thrombolysis for myocardial infarction. *Circulation* 1987;76(suppl II). 18–24.
10 Hogg KJ, Hornung RS, Howie CA, Hockings N, Dunn FG, Hillis WS. Electrocardiographic prediction of coronary artery patency after thrombolytic treatment in acute myocardial infarction: use of the ST segment as a non-invasive marker. *Br Heart J* 1988;60:275–80
11 Chesebro JH, Knatterud G, Roberts R, *et al*. Thrombolysis in myocardial infarction (TIMI) trial, phase 1 a comparison between intravenous tissue plasminogen activator and intravenous streptokinase. *Circulation* 1987; 76 142–54
12 Hirai T, Fujita M, Nakajima H, *et al*. Importance of collateral circulation for prevention of left ventricular aneurysm formation in acute myocardial infarction. *Circulation* 1989;79:791–6.
13 Richardson SJ, Morton P, Murtagh JG, *et al*. Relation of coronary arterial patency and left ventricular function to electrocardiographic changes after streptokinase treatment during acute myocardial infarction. *Am J Cardiol* 1988;61:961–5.
14 Von Essen R, Schmidt W, Uebis R, *et al*. Myocardial infarction and thrombolysis: electrocardiographic short term and long term results using precordial mapping. *Br Heart J* 1985;54:6–10.
15 Bren GB, Wasserman AG, Sheehan FH, Forman S, Dodge HT, Ross AM, for the TIMI investigators. Electrocardiographic evolution during acute myocardial infarction as a correlate of left ventricular functional outcome [Abstract]. *Circulation* 1985;72 (suppl III) 149.

Br Heart J 1990;64:118–20

Enhanced thrombolytic efficacy and reduction of infarct size by simultaneous infusion of streptokinase and heparin

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Abstract

Because paradoxical increase in thrombin activity was reported after the administration of streptokinase in patients with acute myocardial infarction the velocity of reperfusion and degree of myocardial damage were studied when heparin was infused during rather than after streptokinase infusion. Thirty seven consecutive patients with acute myocardial infarction were randomised to receive intravenous heparin during (group 1, n = 18) or after (group 2, n = 19) streptokinase (1·5 megaunits over 60 minutes). Markers of reperfusion were monitored every 15 minutes for 3 hours. The serum concentration of creatine kinase was measured every 2 hours. The two groups were similar in terms of age and sex distribution, infarct site, time to treatment, and baseline myocardial ischaemia. Patients in group 1 had a significantly shorter mean (SD) reperfusion time (57 (35) minutes *v* 101 (47)). From 60 to 120 minutes after randomisation there were significant differences in ST segment elevation between the groups. Serum creatine kinase MB peaked earlier (8 (2) hours) in group 1 than in group 2 (10 (4) hours). The peak concentration was significantly lower in group 1 (87 (47) mU/ml) than in group 2 (134 (96) mU/ml) and infarcts were smaller (25·2 (9·8) gram equivalents/m^2) in group 1 than in group 2 (35·1 (10·2) gram equivalents/m^2).

Simultaneous infusion of heparin and streptokinase speeds up the appearance of signs of reperfusion and reduces infarct size.

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The role of heparin in the treatment of acute myocardial infarction by thrombolysis is still controversial. Some recommend intravenous heparin from the start of thrombolytic treatment,[1 2] and others immediately[3 4] or 2–6 hours[5 6] after the infusion of the thrombolytic agent. Recent large clinical trials of thrombolytic treatment in acute myocardial infarction considered heparin as an option.[7 8] Thrombin concentration increased in acute myocardial infarction[9 10] and again paradoxically after streptokinase or urokinase was given.[11 12]

We studied the thrombolytic efficacy of a simultaneous infusion of streptokinase and heparin in patients with acute myocardial infarction.

Patients and methods

PATIENTS

Patients with ≥ 30 min of ischaemic chest pain (unrelieved by sublingual glyceryl trinitrate) and ST segment elevation (≥ 0·1 mV in two or more standard frontal plane leads or ≥ 0·2 mV in two or more precordial leads) were eligible for the study. Patients were not eligible if more than 3 hours had elapsed since the onset of chest pain. Additional exclusion factors were age > 70 years, uncontrolled hypertension (diastolic pressure > 110 mm Hg; systolic pressure > 200 mm Hg), a cerebrovascular accident within the past 3 months, known haemorrhagic diathesis or active haemorrhage, an important surgical procedure within the past 2 months, previous coronary artery bypass grafting, prolonged cardiopulmonary resuscitation, oral anticoagulant treatment, child-bearing age in women, or serious advanced illness.

TREATMENT PROTOCOL

All patients received an intravenous infusion of streptokinase (1·5 megaunits over 1 h). Each patient was randomly assigned to receive either a simultaneous infusion of heparin (aiming at an activated partial thromboplastin time of 2·0 to 2·5 times normal) (group 1) or saline (group 2). At the end of streptokinase infusion group 2 patients were given heparin (according to the same protocol as group 1). Intravenous heparin was continued for 4–5 days provided that there was no serious bleeding. Subsequently patients were placed on an antiplatelet regimen consisting of aspirin (400 mg per day) and dipyridamole (75 mg three times per day). During the first 24–48 h patients were also given intravenous glyceryl trinitrate to unload the heart and reduce coronary vasomotility.[13] Other medications were prescribed in accordance with the individual's clinical condition.

ASSESSMENT OF REPERFUSION

Before the start of thrombolysis 12 lead electrocardiograms were obtained on a Hewlett Packard cardiograph 4700 A. The amount of myocardium at risk was estimated by the method of Hogg *et al*.[14] The ST segment area was calculated for each lead showing ST elevation and measured as the area above the isoelectric line from the J point to the end of the T wave. The sum of scores for all leads provided an index of myocardial ischaemia. Patients were asked to grade the intensity of chest pain from 0 to 100 on a visual analogue scale. Then the 12 lead electrocardiograms and the intensity of chest pain were monitored every 15 min for 3 hours and also whenever there was a change in symptoms, ST segment shift on the monitor, or in cardiac rhythm. Blood samples were drawn to measure serum creatine kinase MB every second hour during the first 16 hours and then every fourth hour for the next 24 hours. Then serum creatine kinase MB was measured once daily until it became normal.

To speed up the initial treatment we chose to recognise reperfusion non-invasively. Reperfusion was considered to have occurred when there was a gradual reduction in the size of the ST segment shift to <50% of the basal value accompanied by a sudden or gradual lessening of chest pain and a rapid rise in the serum concentration of creatine kinase MB with a peak within 13 hours of the onset of chest pain. The interval to reperfusion (reperfusion time) was measured from the start of thrombolysis to the onset of the resolution of the ST segment elevation. All the electrocardiograms, the records of the course of chest pain, and the enzymatic time-activity curves were analysed by two investigators who were unaware of the patient's treatment group. This non-invasive method has been validated by angiography[15-18] and is currently used in clinical trials.[19 20] Infarct size was measured according to Sobel *et al.*[21] Several experimental and clinical studies showed that measurement of infarct size by enzyme tests is feasible and meaningful after thrombolysis.[22-24]

STATISTICAL ANALYSIS

All values are expressed as mean (SD). Paired and unpaired *t* tests were used to compare the means of continuous variables. χ^2 tests (with Yates's correction when indicated) were used to compare discontinuous variables. ST segment changes as a function of time were analysed by ANOVA. A two tailed method and a 0·05 level of statistical significance were used throughout.

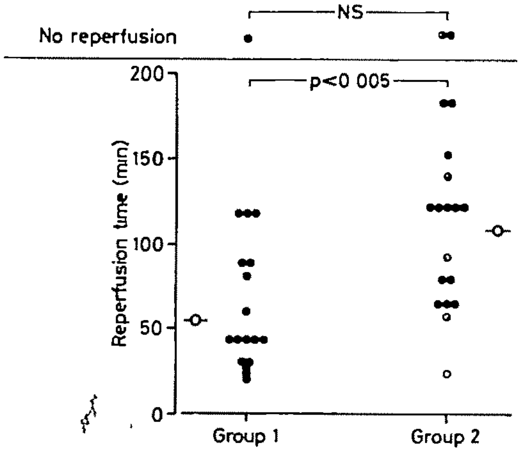


Figure 1 Reperfusion time after simultaneous (group 1) or subsequent (group 2) addition of heparin to streptokinase infusion

Results

Thirty seven patients were randomly allocated to be treated with streptokinase plus simultaneous heparin (n = 18, group 1) or streptokinase followed by heparin (n = 19, group 2). Baseline characteristics were similar in the two groups (table). In particular the degree of evidence of ischaemia on the electrocardiogram at presentation was similar in both groups (the ST segment area was 112 (62) mm^2 in group 1 and 120 (58) mm^2 in group 2; p = NS). Blinded assessment showed that 17 of the 18 patients in group 1 and 17 of the 19 patients in group 2 had non-invasive signs of reperfusion. Reperfusion time was significantly shorter in group 1 (57 (35) min *v* 101 (47) min; $p < 0·005$) (fig 1). Figure 2 shows the time course of ST segment elevation. In most patients there were no statistically significant differences between the two groups up to 45 minutes after randomisation. At 60 minutes group 1 patients showed a significantly lower ST segment elevation ($p < 0·05$). The difference remained significant up to 120 minutes.

The time to peak creatine kinase MB was 8 (2) h in group 1 and 10 (4) h in group 2 ($p < 0·05$). On average the peak concentration of creatine kinase MB was 87 (47) mU/ml in group 1 and 134 (96) mU/ml in group 2 ($p < 0·05$). The infarct was significantly smaller in group 1 (25·2 (9·8) g equivalents/m^2) than in group 2 (35·1 (10·2) g equivalents/m^2) ($p < 0·05$).

Many patients developed skin haematomas. Three patients (16·6%) in group 1 and six (31·5%) in group 2 had major bleeding com-

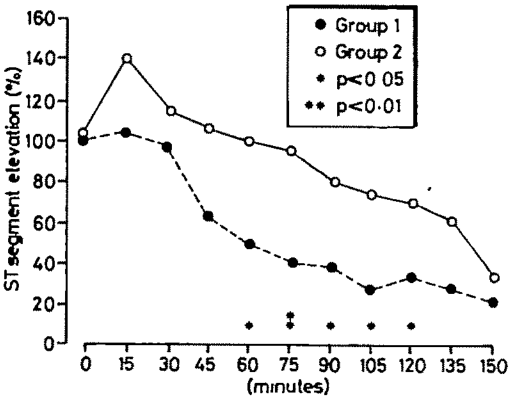


Figure 2 Time course of ST segment elevation in the two groups (percentage change v baseline).

Baseline characteristics of patients in study groups

	Group 1	*Group 2*
Number	18	19
Age (year)	59 (8)	60 (8)
Female (%)	11·1	26 3
Hypertension (%)	27·7	31 6
Diabetes (%)	22·2	15·8
Smoker (%)	77·7	78·9
Hypercholesterolaemia (%)	26·3	
Anterior MI (%)	50	52 6
Inferior MI (%)	50	47 4
Prior MI (%)	16·6	15 8
Mean (SD) time to treatment (min)	115 (48)	118 (50)
Mean (SD) ST segment area (mm^2)	112 (62)	120 (58)

MI, myocardial infarction.
None of the variables was significantly different in the two groups.

plications. Overall, the primary bleeding site was in the genitourinary tract in seven patients and at the point of puncture for cardiac catheterisation in two patients. Five patients in group 1 and six in group 2 had early postinfarction angina. There was a reinfarction (documented by recurrence of prolonged chest pain along with typical electrocardiographic changes and a new increase in creatine kinase MB) in one patient in group 1 and two in group 2.

Discussion

Acute myocardial infarction is associated with increased thrombin activity.[9,10] The main effects of thrombin include platelet activation, fibrin formation, and impairment of fibrinolysis.[25,26] Other important effects include the stabilisation of fibrin polymers and disturbance of endothelial cells that results in tissue factor induction and binding of neutrophils.[27,28] Evidence is now accumulating that the administration of streptokinase leads to an immediate, paradoxical increase in thrombin activity.[11,12] This effect has several explanations. Firstly, removal of the thrombus may expose the thrombogenic surface of the infarct vessel. Reperfusion of ischaemic myocardium may be associated with a washout of thromboplastic material. Finally, thrombin absorbed on to the fibrin clot may be released by thrombolytic treatment and regain its activity. So there are strong theoretical reasons for giving heparin with streptokinase. But the possibility of bleeding complications has prevented heparin being regarded as mandatory in some recent large scale clinical trials.[7,8]

Our study shows that when heparin treatment is given there is a clear advantage in infusing it with rather than after streptokinase. This conclusion is supported by the quicker resolution of electrocardiographic signs of ischaemia and by the earlier peaking of serum concentrations of creatine kinase MB. These signs of faster reperfusion[15,18] were associated with a significantly lower peak value of serum creatine kinase and a smaller infarct. Earlier studies by our group in which serum creatine kinase MB was measured frequently showed a good correlation between left ventricular function and both enzymatically assessed infarct size and the extension of resting thallium-201 perfusion defects (measured by single-photon emission tomography).[24,29]

The reduction of infarct size that we saw in the present study when heparin was given early was the result of a mean reduction of 44 minutes in the time to reperfusion. These data confirm that the human heart is very sensitive to the duration of ischaemia before reperfusion and support the concept that reperfusion strategies should also take account of the speed of reperfusion.

1 ISAM. A prospective trial of intravenous streptokinase in acute myocardial infarction. *N Engl J Med* 1986;314.1465–71.

2 O'Rourke M, Baron D, Keogh A Limitation of myocardial infarction by early infusion of recombinant tissue-type plasminogen activator. *Circulation* 1988,77:1311–5.

3 Ganz W, Geft I, Maddahi I, *et al* Nonsurgical reperfusion in evolving myocardial infarction *J Am Coll Cardiol* 1983;1:1247–53

4 White HD, Norris RM, Brown MA, *et al.* Effect of intravenous streptokinase on left ventricular function and early survival after acute myocardial infarction. *N Engl J Med* 1987;317:850–5.

5 Kennedy JW, Martin GV, Davis KB, *et al* The Western Washington intravenous streptokinase in acute myocardial infarction randomised trial. *Circulation* 1988;77: 345–52.

6 AIMS Trial Study Group. Effect of intravenous APSAC on mortality after acute myocardial infarction preliminary report of a placebo-controlled clinical trial. *Lancet* 1988,i:545–9

7 Grupp Italiano per lo Studio della Streptochinasi nell' Infarto miocardico (GISSI) Effectiveness of intravenous thrombolytic treatment in acute myocardial infarction *Lancet* 1986,i:397–401.

8 ISIS-2 (Second International Study of Infarct Survival) collaborative group. Randomized trial of intravenous streptokinase, oral aspirin, both, or neither among 17187 cases of suspected acute myocardial infarction *Lancet* 1988;ii·349–60

9 Neri Serneri GG, Gensini GF, Abbate R, *et al.* Increased fibrinopeptide A formation and thromboxane A_2 production in patients with ischaemic heart disease: relationships to coronary pathoanatomy, risk factors, and clinical manifestations. *Am Heart J* 1981;101:185–94.

10 Small M, Lowe GDO, Dougals JT, Hutton I, Lorimer AR, Forbes CD. Thrombin and plasmin activity in coronary artery disease. *Br Heart J* 1988;60:201–3

11 Seitz R, Blanke H, Pratorius G, Strauer BE, Egbring R. Increased thrombin activity during thrombolysis. *Thromb Haemost* 1988,59:541–2.

12 Eisemberg PR, Sherman LA, Jaffe AS. Paradoxic elevation of fibrinopeptide A after streptokinase. evidence for continued thrombosis despite intense fibrinolysis. *J Am Coll Cardiol* 1987;10 527–9.

13 Tymchak WJ, Michorowski BL, Burton JR. Preservation of left ventricular function and topography with combined reperfusion and intravenous nitroglycerin in acute myocardial infarction [Abstract]. *J Am Coll Cardiol* 1988;11:90.

14 Hogg KJ, Lees KR, Hornung RS, Howie CA, Dunn FG, Hillis WS Electrocardiographic evidence of myocardial salvage after thrombolysis in acute myocardial infarction. *Br Heart J* 1989,61 489–95.

15 Gore JM, Roberts R, Ball SP, Montero A, Goldberg RJ, Dalen JE. Peak creatine kinase as a measure of effectiveness of thrombolytic therapy in acute myocardial infarction. *Am J Cardiol* 1987,59:1234–8.

16 Krucoff MN, Green CE, Satler LF, *et al.* Noninvasive detection of coronary artery patency using continuous ST segment monitoring. *Am J Cardiol* 1986;57:916–22.

17 Garabedian HD, Gold HK, Yasuda T, *et al.* Detection of coronary artery reperfusion with creatine kinase-MB determinations during thrombolytic therapy correlation with acute angiography *J Am Coll Cardiol* 1988,11: 729–34.

18 Hogg KJ, Hornung RS, Howie CA, Hockings N, Dunn FG, Hillis WS. Electrocardiographic prediction of coronary artery patency after thrombolytic treatment in acute myocardial infarction. use of the ST segment as a non-invasive marker *Br Heart J* 1988;60·275–80.

19 Ganz W, Geft I, Shah PK, *et al.* Intravenous streptokinase in evolving acute myocardial infarction. *Am J Cardiol* 1984,53.1209–16.

20 Magnani B. Plasminogen Activator Italian Multicenter Study (PAIMS). Comparison of intravenous recombinant single-chain human tissue-type plasminogen activator (rt-PA) with intravenous streptokinase in acute myocardial infarction *J Am Coll Cardiol* 1989;13·19–26.

21 Sobel BE, Roberts R, Larson KB. Estimation of infarct size from serum MB creatine phospokinase activity· applications and limitations. *Am J Cardiol* 1976;37.474–85.

22 Dé Zwaan C, Willems GM, Vermeer F, *et al.* Enzyme tests in the evaluation of thrombolysis in acute myocardial infarction. *Br Heart J* 1988,59:175–83.

23 Van der Laarse A, Vermeer F, Hermens WT, *et al.* Effects of early intracoronary streptokinase on infarct size estimated from cumulative enzyme release rate. a randomised trial of 533 patients with acute myocardial infarction. *Am Heart J* 1986;112.672–81.

24 Melandri G, Tartagni F, Branzi A, *et al.* La stima enzimatica dell'area infartuale nei pazienti sottoposti a terapia trombolitica. *Cardiologia* 1988;33:61–7

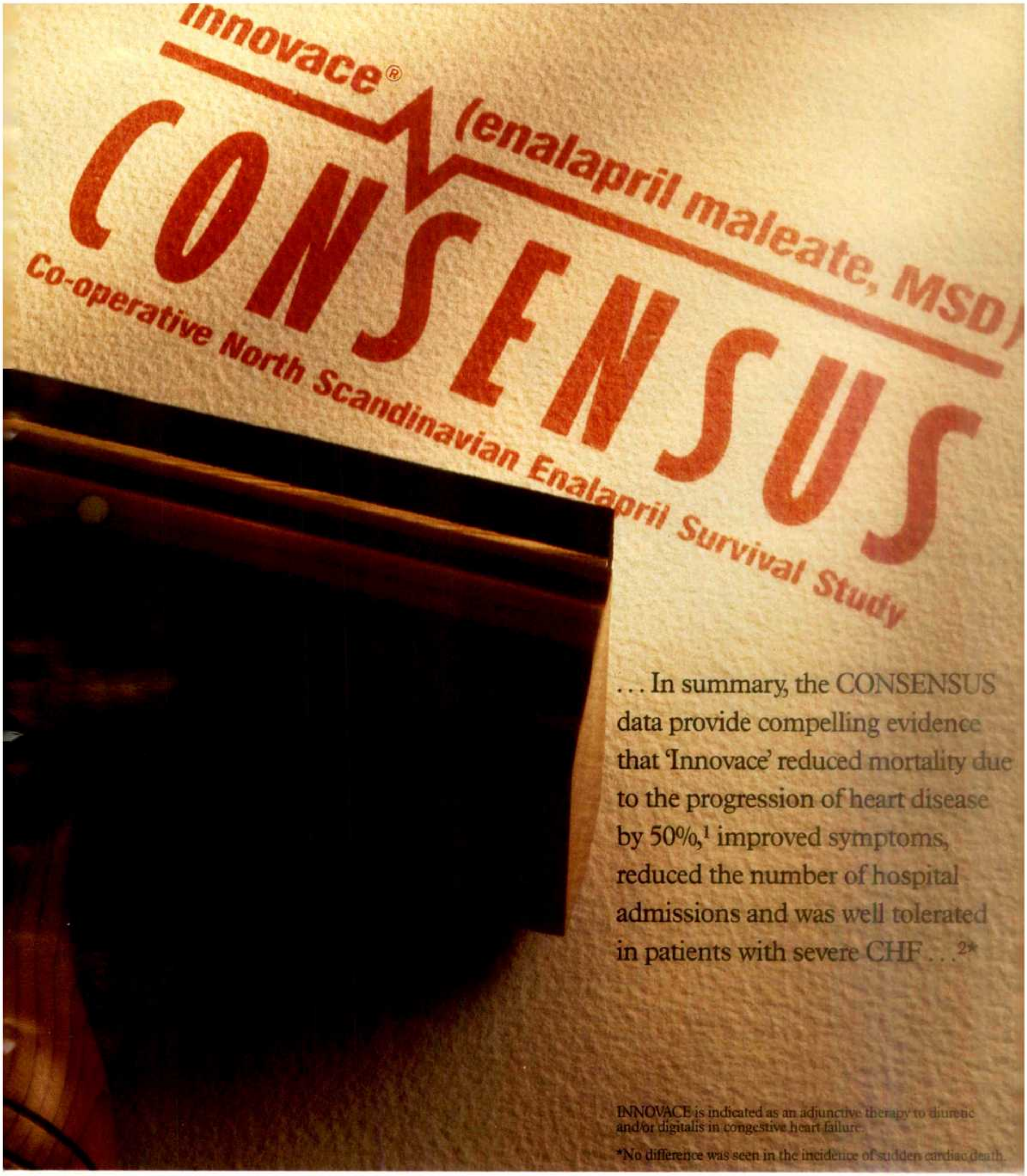
25 Gelehrter TD, Sznycer-Laszuk R. Thrombin induction of plasminogen activator-inhibitor in cultured human endothelial cell. *J Clin Invest* 1986;77:165–9.

26 Konkle BA, Ginsburg D. The addition of endothelial cell growth factor and heparin to human umbilical vein endothelial cell cultures decreases plasminogen activator inhibitor-1 expression *J Clin Invest* 1988,82:579–85.

27 Nawroth PP, Stern DM. Endothelial cell procoagulant properties and the host response. *Semin Thromb Hemost* 1987,13:391–7

28 Whatley RE, Zimmerman GA, McIntyre TM, Taylor R, Prescott SM. Production of platelet-activating factor by endothelial cells. *Semin Thromb Hemost* 1987;13:445–53.

29 Melandri G, Tartagni F, Branzi A, *et al.* Left ventricular volume response to exercise after thrombolytic therapy: relationship with tomographic and enzymatic infarct size. *C V World Rep* 1988,1:29–33.



. . . In summary, the CONSENSUS data provide compelling evidence that 'Innovace' reduced mortality due to the progression of heart disease by 50%,[1] improved symptoms, reduced the number of hospital admissions and was well tolerated in patients with severe CHF . . .[2*]

INNOVACE is indicated as an adjunctive therapy to diuretic and/or digitalis in congestive heart failure.

*No difference was seen in the incidence of sudden cardiac death.

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efer to Data Sheet before prescribing.
NDICATIONS
ypertension where standard therapy is ineffective r inappropriate. Congestive heart failure (adjunc-ve therapy).
OSAGE AND ADMINISTRATION
ypertension: Initially 5 mg once daily, reduce tarting dose to 2.5 mg if over 65 years, on diuretics r renally impaired. Adjust dose according to esponse; maintenance usually 10-20 mg once aily. Maximum dose 40 mg daily. Diuretic-treated atients – if possible stop diuretic two to three ays before starting 'Innovace'. Resume diuretic ter if required.
ongestive heart failure (adjunctive therapy): Initially, 5 mg daily in hospital under medical supervision, ncreasing to the usual maintenance dose of 10-20 ng once daily according to response.
mpaired renal function: May require a lower naintenance dose. 'Innovace' is dialysable.
ONTRA-INDICATIONS
regnancy – stop therapy if suspected. Hyper-ensitivity to 'Innovace'. Patients reacting with ngioneurotic oedema to previous ACE-inhibitor reatment.

PRECAUTIONS
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Renal insufficiency; renovascular hypertension; possibility of hypotension especially in ischaemic heart disease or cerebrovascular disease; surgery/anaesthesia.
Combination with antihypertensives may increase hypotensive effect. Sometimes increased blood urea and creatinine and/or cases of renal insufficiency if given with diuretics. Minimises thiazide-induced hypokalaemia and hyperuricaemia. Potassium supplements, potassium-sparing diuretics, and potassium-containing salt substitutes are not recommended. Possible reduced response in Afro-Caribbean patients. Use with caution in breast-feeding mothers. Do not use in aortic stenosis, or outflow tract obstruction. Monitor serum levels of lithium, if lithium salts are given.
SIDE EFFECTS
Dizziness, headache. Others include fatigue, asthenia, nausea, diarrhoea, muscle cramps, rash, dysgeusia, cough.
Less commonly, angioneurotic oedema; other hypersensitivity reactions; renal failure; symptomatic hypotension (especially if volume-depleted); severe hypotension (more likely if severe heart failure); hyperkalaemia; hypokalaemia; increases in liver enzymes and serum bilirubin (usually reversible on discontinuation of 'Innovace'); paraesthesiae; impotence.

BASIC NHS COST
2.5 mg tablets, £10.00 for bottles of 50.
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Issued December 1989.

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References
1. CONSENSUS Trial Study Group, *New Engl. J. Med.*, 1987, **316**, 1429.
2. Kjekshus, J., and Swedberg, K., *Amer. J. Cardiol.*, 1988, **62**, 67A-72A.

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Br Heart J 1990;64:121–8

Measurement of cardiac reserve in cardiogenic shock: implications for prognosis and management

Lip-Bun Tan, William A Littler

Abstract

The hypothesis that the prognosis of cardiogenic shock patients is primarily dependent on cardiac pumping reserve was tested in a prospective study of 28 consecutive patients clinically diagnosed to be in cardiogenic shock and treated medically. Haemodynamic function was assessed by thermodilution Swan-Ganz catheters and arterial cannulas. The cardiac pumping reserve was evaluated by the response of the failing heart to graded incremental dobutamine infusion (2·5 to 40 μg/kg/min) after optimalising the left ventricular preload. Eleven of the patients survived for more than the one year of follow up and the rest died. Haemodynamic evaluation during the basal resting state was only able to identify unambiguously non-survivors whose cardiac function was most severely compromised. Survivors and non-survivors with higher values were indistinguishable by basal haemodynamic criteria. The response to dobutamine stimulation clearly separated the cardiac pump function of survivors and those who died. All patients with peak cardiac power output of <1·0 W or peak left ventricular stroke work index of <0·25 J/m^2 died whereas all those with higher values lived for more than a year.

Thus this study showed that haemodynamic evaluation of cardiac reserve can provide objective criteria for predicting outcome in individual patients with cardiogenic shock. The availability of such a prognostic indicator will be invaluable in formulating management plans for these patients.

Patients with cardiogenic shock have a poor prognosis. Reported mortality varies from 73% to 100%.[1] The diagnosis of cardiogenic shock raises the dilemma of whether or not to resort to aggressive intervention.[2] Newer treatments, such as prosthetic ventricles and cardiac transplantation,[3-5] can improve the outcome in some patients. Not all patients require these interventions. Can those patients who will survive cardiogenic shock treated medically be identified by a simple physiological test?

The reserve of the cardiac pump is a major determinant of survival in patients with cardiogenic shock. We examined whether cardiac reserve correlated with prognosis. In cardiogenic shock the basal resting performance of the heart may be appreciably depressed, but if there is sufficient reserve it is likely that the heart will recover and function adequately again. To evaluate cardiac reserve fully the heart has to be stimulated to enhance its performance by increasing the heart rate, preload, and contractility from basal values.

In cardiogenic shock, preload reserve is either fully used (with considerably increased left ventricular filling pressure) or inconsequential (because of the flattened Starling curve). However, in a few patients there may be relative hypovolaemia.[6] Careful fluid challenge would show the amount of reserve present; those with limited preload reserve had a poorer prognosis.[7 8] Inotropic and chronotropic stimulation with dobutamine was used to assess cardiac pumping reserve in a group of patients with severe heart failure; the information was of prognostic value.[9] The aim of the present study was to investigate whether similar information about cardiac reserve can be obtained by dobutamine stimulation in patients with cardiogenic shock, after optimalising the preload. A prospective study was conducted to test the hypothesis that in cardiogenic shock the magnitude of cardiac pumping reserve is predictive of outcome.

Patients and methods

PATIENTS

We studied patients admitted to the coronary care unit in East Birmingham Hospital between September 1984 and June 1986 with clinical manifestations of cardiogenic shock. All patients who fulfilled the selection criteria described below were included. The syndrome of shock was diagnosed according to Cohn's criteria.[10] All the patients had at least two of the clinical features of shock: oliguria with urine output <20 ml/hour, cool moist skin, auscultatory systolic blood pressure <90 mm Hg, obtunded mental state, metabolic acidosis.

We excluded patients with all other causes of shock including those attributable to arrhythmias that were not controlled and to drugs (for example opiates). We excluded relative hypovolaemia by showing that fluid challenge did not lead to any improvement in cardiac performance in patients in whom right ventricular infarction was suspected or pulmonary wedge pressure was <18 mm Hg. Patients with complete heart block were paced before entry into the study. Since one of the

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aims of this study was to determine objectively which patient should be treated with ventricular assist devices or emergency cardiac surgery, only patients treated medically were included—that is those who were not suitable for surgery or those who refused surgery and insertion of intra-aortic counterpulsation balloon pumps. None of the patients had angina pectoris, papillary muscle dysfunction or rupture, ventricular septal defect or ventricular rupture, and none was treated with thrombolytic agents. Twenty eight patients (seven women, 21 men; mean age 59 (range 36–73)) fulfilled the above criteria. In 24 patients cardiogenic shock developed after acute myocardial infarction (established by appropriate history and clinical observations, in association with documented electrocardiographic evidence of infarction and serial changes in serum enzyme concentrations) and in four shock developed after exacerbation of chronic cardiac failure caused by ischaemic heart disease. These four patients were included because we wanted to include all patients with true cardiogenic shock irrespective of cause, who fulfilled the selection criteria.

PROTOCOL

As part of the standard management of patients with cardiogenic shock, thermodilution Swan-Ganz catheters and arterial cannulas were inserted, and these provided readings of right atrial (RAP), mean systemic arterial (MBP), pulmonary arterial (PAP) and wedge (PAWP) pressures, and cardiac output (CO, measured in triplicate). The heart rate (HR) was obtained from the electrocardiogram. The left ventricular ejection fraction (LVEF) at basal resting state was estimated by cross sectional echocardiography.

The following equations were used to calculate the haemodynamic variables (all pressures were measured in mm Hg and cardiac output (CO) in $1.min^{-1}$: cardiac index (CI = CO/body surface area, $1.min^{-1}.m^{-2}$); stroke volume index (SVI = CI/HR, $ml.m^{-2}$); left ventricular stroke work index (LVSWI = (MBP-PAWP) × SVI × 0·133 ($J.m^{-2}$), conversion to $g.m.m^{-2}$ by multiplication by 102·04); systemic vascular resistance (SVR = (MBP − mean RAP)/CO × 8, $kPa.s.l^{-1}$, conversion to $dyn.s.cm^{-5}$ by multiplication by 10); pulmonary vascular resistance (PVR = (mean PA pressure − mean PAW pressure) × CO × 8, $kPa.s.l^{-1}$); cardiac power output (CPO = (MBP − RAP) × CO × 2·2167 × 10^{-3}W).

Dobutamine infusion was indicated in all patients on clinical grounds. A dose titration of dobutamine was used to assess the haemodynamic response (doses from 2·5 μg/kg/min increased by 2·5 or 5·0 μg/kg/min to a maximum of 15–40 μg/kg/min every 5–10 min). Maximum stimulation was assumed when there was no further rise in cardiac power output.

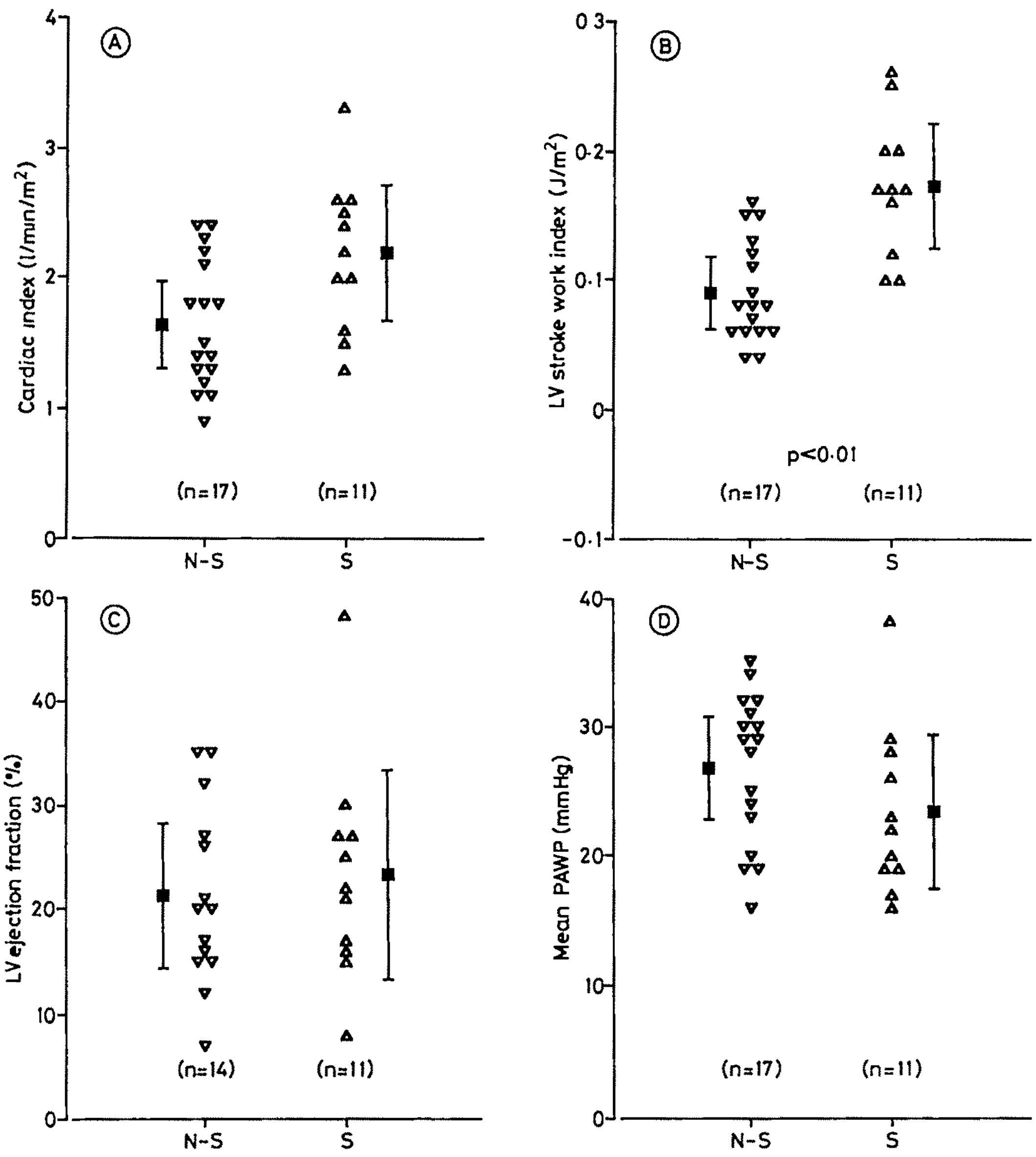
The patients were followed up for at least a year. Those who survived for more than a year were termed "survivors" and those who did not the "non-survivors". We selected this follow up period because we knew that the final events leading to death are unpredictable, and that the interval between shock and death may be short when the terminal event is arrhythmia or longer when death is due to cardiac cachexia or renal failure. During the follow up, heart failure was treated conventionally with diuretics, digoxin, and vasodilators. To test the hypothesis that indicators of cardiac pumping reserve were predictive of outcome we compared haemodynamic function at basal resting state and during maximal dobutamine stimulation in survivors with that in those who died.

Table 1 Clinical and baseline haemodynamic data in individual patients

Case No	Age yr	Sex	BSA (m^2)	Aetiology of cardiogenic shock	Survived/died	Time to death	LVEF (%)	HR	RAP	PAWP	CI	SVI	LVSWI	CPO
1	62	M	1·50	IHD, E-CCF	Died	12 wks	12	86	17	23	2·4	27·9	14·9	0·37
2	56	M	1·70	AMI, LVF	"	2 days	—	71	18	19	1·2	16·6	6·4	0·13
3	72	F	1·60	AMI, BVF	"	2 days	—	140	30	30	1·4	9·8	3·9	0·15
4	48	M	1·72	AMI, LVF	"	1 day	35	115	8	29	2·2	18·7	12·2	0·57
5	64	M	1·84	AMI, CCF	"	9 days	20	132	20	32	1·8	13·6	6·3	0·34
6	64	F	1·50	AMI, BVF	"	1 day	27	93	26	31	0·9	10·0	5·8	0·15
7	52	M	1·71	AMI, LVF	"	6 wks	26	101	9	19	2·1	20·8	16·4	0·55
8	63	M	1·79	AMI, LVF	"	3 days	15	112	18	32	1·4	12·5	7·6	0·33
9	46	M	1·82	AMI, CCF	"	4 days	21	117	16	28	2·4	20·2	12·6	0·56
10	64	F	1·62	AMI, LVF, CHB	"	2 days	32	110	13	16	1·1	10·1	6·2	0·20
11	59	M	1·92	IHD, E-CCF	"	17 days	20	80	22	34	1·1	14·3	6·3	0·22
12	64	F	1·60	AMI, BVF	"	1 day	7	63	20	29	1·3	19·8	5·6	0·13
13	64	M	1·82	AMI, LVF	"	2 days	—	100	15	30	1·5	14·8	4·0	0·21
14	62	F	1·76	AMI, LVF	"	1 day	15	136	14	25	1·8	13·0	7·9	0·39
15	63	M	2·05	AMI, LVF	"	7 days	35	95	18	20	1·8	19·0	14·7	0·49
16	69	F	1·60	AMI, LVF, CHB	"	2 days	16	90	14	24	1·3	14·6	8·0	0·24
17	54	M	1·72	AMI, CCF	"	8 days	17	109	4	35	2·3	21·3	13·4	0·69
18	51	M	2·30	AMI, LVF	Survivor	> 1 yr	30	109	14	19	1·5	13·6	10·5	0·47
19	55	M	1·90	AMI, RVMI, LVF	"	> 1 yr	25	97	20	28	2·6	27·1	15·9	0·58
20	67	F	1·50	AMI, LVF	"	> 1 yr	27	75	5	16	2·5	32·9	25·4	0·57
21	55	M	1·86	AMI, LVF	"	> 1 yr	16	98	7	20	2·4	24·1	17·1	0·64
22	40	M	1·86	AMI, RVMI, LVF	"	> 1 yr	48	80	21	19	2·6	32·9	19·8	0·47
23	73	M	1·81	AMI, LVF	"	> 1 yr	22	80	8	17	2·2	27·6	19·5	0·55
24	51	M	1·88	IHD, E-CCF	"	> 1 yr	17	92	18	29	1·6	17·9	11·9	0·42
25	68	M	1·78	IHD, E-CCF	"	> 1 yr	8	55	18	26	2·0	35·8	25·7	0·48
26	36	M	1·94	AMI, LVF	"	> 1 yr	27	91	12	22	1·3	14·7	10·2	0·36
27	68	M	1·78	AMI, LVF	"	> 1 yr	15	97	17	38	3·3	33·6	16·6	0·75
28	63	M	1·72	AMI, LVF	"	> 1 yr	21	77	10	23	2·0	26·4	16·6	0·47

AMI, acute myocardial infarction; BSA, body surface area; BVF, biventricular failure; CCF, chronic cardiac failure; CHB, complete heart block; E-CCF, exacerbation of CCF, IHD, ischaemic heart disease; LVF, left ventricular failure, RVMI, right ventricular myocardial infarction.
See footnote to table 2 for abbreviations and units for haemodynamic variables.

Figure 1 Resting haemodynamic data of survivors (S) v non-survivors (N-S): (A) cardiac index, (B) left ventricular stroke work index, (C) left ventricular ejection fraction, (D) mean pulmonary artery wedge pressure (PAWP). Mean values and 99% confidence intervals are shown.



STATISTICAL ANALYSIS

We used Bonferroni's analysis of variance to compare the differences between survivors and non-survivors and a paired *t* test to assess the significance of changes brought about by dobutamine. Differences were regarded as significant at $p < 0{\cdot}01$. Results were expressed as means (SEM).

Results

MORTALITY

Table 1 shows the clinical data and survival of the patients. These 28 cardiogenic shock patients were clinically indistinguishable and were all considered to have a grave prognosis before the haemodynamic study. Seventeen died during follow up. All but two of these patients died of progressive cardiac failure while in hospital, within 3 weeks of the diagnosis of shock. The average time between diagnosis of shock and death in hospital was 4 days. One of the two exceptions died at home after 10 weeks of progressive heart failure (New York Heart Association class IV throughout). The other was discharged in New York Heart Association class III but was readmitted 4 weeks later and died of intractable ventricular tachycardia. The eleven survivors lived more than a year and were in New York Heart Association class III or better when reviewed at six months and one year after discharge from hospital.

BASAL HAEMODYNAMIC DATA

Table 1 and fig 1 show the baseline haemodynamic data of individual patients. The mean (SEM) left ventricular ejection fraction at basal resting state for the entire group was 22·2 (1·9)%. Table 2 shows the mean basal haemodynamic values for all the patients. The data suggested that ventricular performance was more depressed in those who died, though only the left ventricular stroke work index was significantly different in the two groups. Figure 1A identifies a clear subset of four patients who died, defined by resting cardiac index of $<1{\cdot}3$ l.min^{-1}.m^{-2}. Although patients with a resting cardiac index of between 1·3 and 2·4 l.min^{-1}.min^{-2} were also at high risk several within this range survived. Similarly, all (11) patients with basal left ventricular stroke work index $<0{\cdot}1$ J.m^{-2} died (fig 1B), whereas all those with stroke work index >0 16 J.m^{-2}

Table 2 Haemodynamic response (mean (SEM)) to peak dobutamine infusion

		All patients	*Survivors*	*Non-survivors*
HR:	Basal	96·5 (3·8)	86·5 (4·3)	102·9 (5·1)
	Peak	111·4 (3·6)**	106·3 (4·7)**	114·7 (4·9)*
RAP:	Basal	15·4 (1·1)	13·6 (1·6)	16·6 (1·5)
	Peak	12·8 (1·2)*	11·5 (2·0)	13·6 (1·4)*
MPAP:	Basal	36·1 (1·7)	35·9 (2·7)	36·2 (2·1)
	Peak	35·9 (1·9)	33·8 (3·3)	37·2 (2·3)
PAWP:	Basal	25·5 (1·1)	23·4 (1·9)	26·8 (1·4)
	Peak	23·7 (1·5)	18·8 (2·2)	26·8 (1·7)
MBP:	Basal	69·8 (1·7)	73·5 (1·3)	67·4 (2·5)
	Peak	80·1 (2·6)**	88·3 (3·2)*	74·8 (3·1)*
CI:	Basal	1·9 (0·1)	2·2 (0·2)	1·6 (0·1)
	Peak	3·0 (0·2)**	4·0 (0·1)**‡	2·4 (0·1)**
SVI:	Basal	20·1 (1·4)	26·1 (2·2)	16·3 (1·2)
	Peak	28·3 (2·0)**	38·7 (2·0)**‡	21·6 (1·5)**
LVSWI:	Basal	12·2 (1·1)	17·2 (1·5)†	9·0 (1·0)
	Peak	22·2 (2·2)**	35·2 (1·3)**‡	13·7 (1·2)**
CPO:	Basal	0·41 (0·03)	0·52 (0·03)	0·34 (0·04)
	Peak	0·84 (0·07)**	1·25 (0·04)**‡	0·57 (0·05)**
PVR:	Basal	26·5 (2·6)	26·2 (3·4)	26·6 (3·6)
	Peak	18·5 (1·7)**	16·1 (2·0)**	20·0 (2·4)
SVR	Basal	141·4 (8·2)	127·4 (10·6)	150·5 (11·0)
	Peak	109·1 (7·1)**	85·1 (6·2)*	124·6 (9·1)

*p < 0·01 and **p < 0·001, basal *v* peak.
†p < 0·01 and ‡p < 0·001, survivors *v* non-survivors.
CI, cardiac index ($l.min^{-1}.m^{-2}$); CPO, cardiac power output (W); HR, heart rate (beats/min); LVSWI, left ventricular stroke work index (10^{-2} $J.m^{-2}$); MBP, mean systemic arterial pressure (mm Hg); MPAP, mean pulmonary artery arterial pressure (mm Hg); PAWP, pulmonary artery wedge pressure (mm Hg); PVR, pulmonary vascular resistance ($kPa.s.l^{-1}$); RAP, right atrial pressure (mm Hg); SVI, stroke volume index ($ml.m^{-2}$); SVR, systemic vascular resistance ($kPa.s.l^{-1}$).

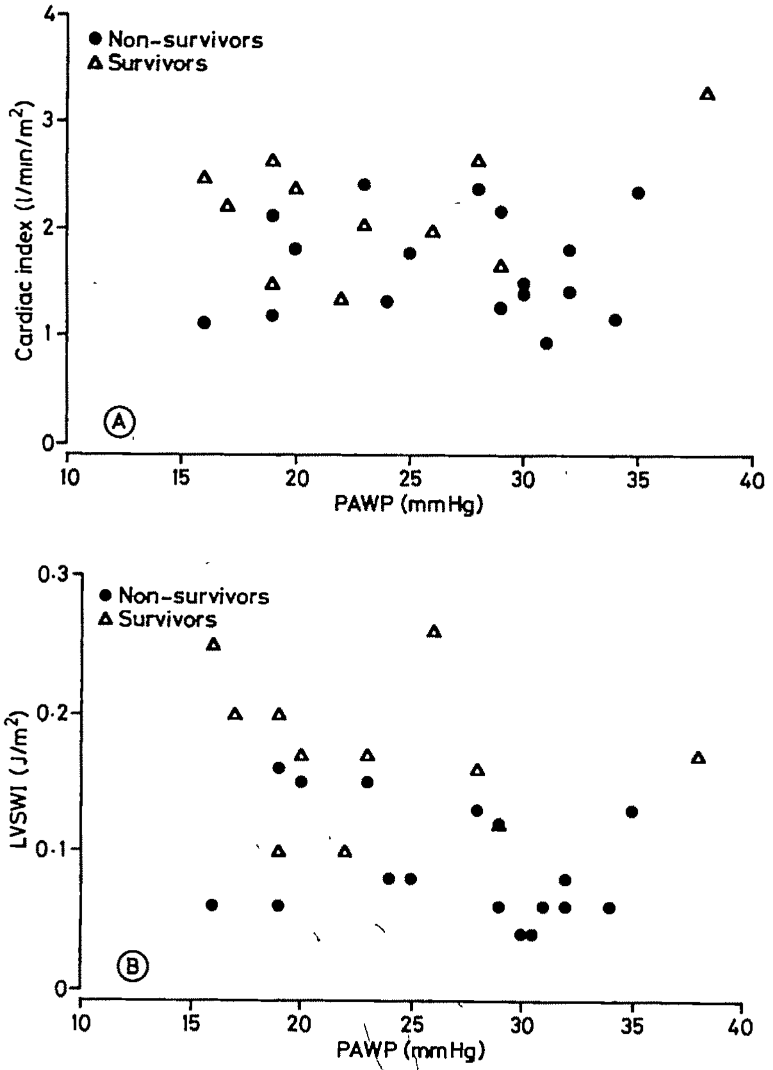


Figure 2 Relation between (A) cardiac index and mean pulmonary artery wedge pressure (PAWP) and (B) left ventricular stroke work index (LVSWI) and pulmonary artery wedge pressure at basal resting states.

survived; between these two values the results overlapped. In figs 1C and D the overlap of the values for pulmonary artery wedge pressure and left ventricular ejection fraction were even more conspicuous and values of the two groups were not significantly different.

A basal left ventricular filling pressure > 15 mm Hg and a cardiac index < 2·3 $l.min^{-1}.m^{-2}$ were defined by Ratshin and colleagues in 1972 as criteria identifying the subset who will all die,[7] but several survivors in our patient population had values in this range. Similarly, the relation between left ventricular stroke work index and filling pressure at rest, used to identify high risk cases in Vincent *et al*'s study,[11] did not clearly separate the survivors from the non-survivors (fig 2).

RESPONSE TO INOTROPIC STIMULATION

After optimalisation of the preload (by fluid challenge until there was no further rise in cardiac output or cardiac power output), cardiac reserve was assessed by noting the response to inotropic stimulation by dobutamine infusion. Figures 3A and B show the cardiac index and power output of four representative patients from the survivor and non-survivor subsets. Both the cardiac index and power output increased with dobutamine dosages. At the peak dosages further increases

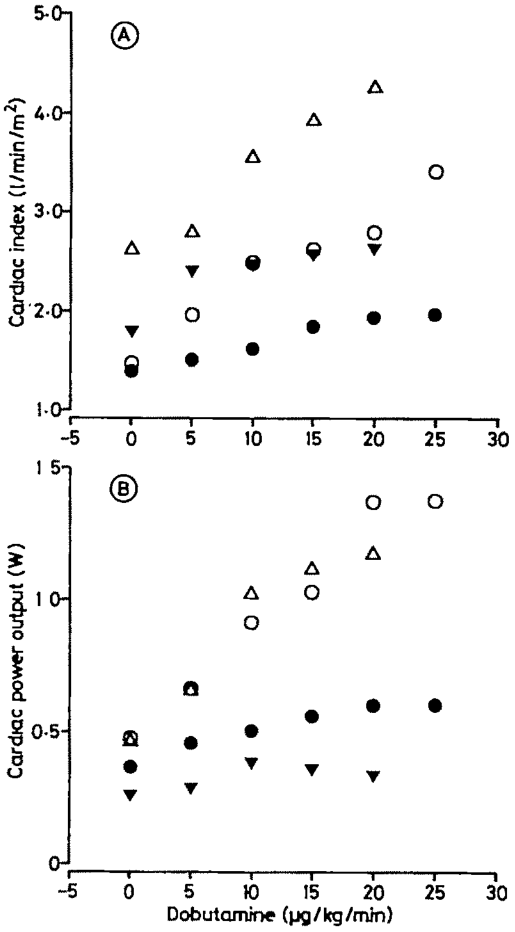


Figure 3 Responses to incremental dobutamine infusion in terms of (A) cardiac index and (B) cardiac power output Each symbol represents the responses of an individual patient (open symbols for survivors and filled symbols for non-survivors).

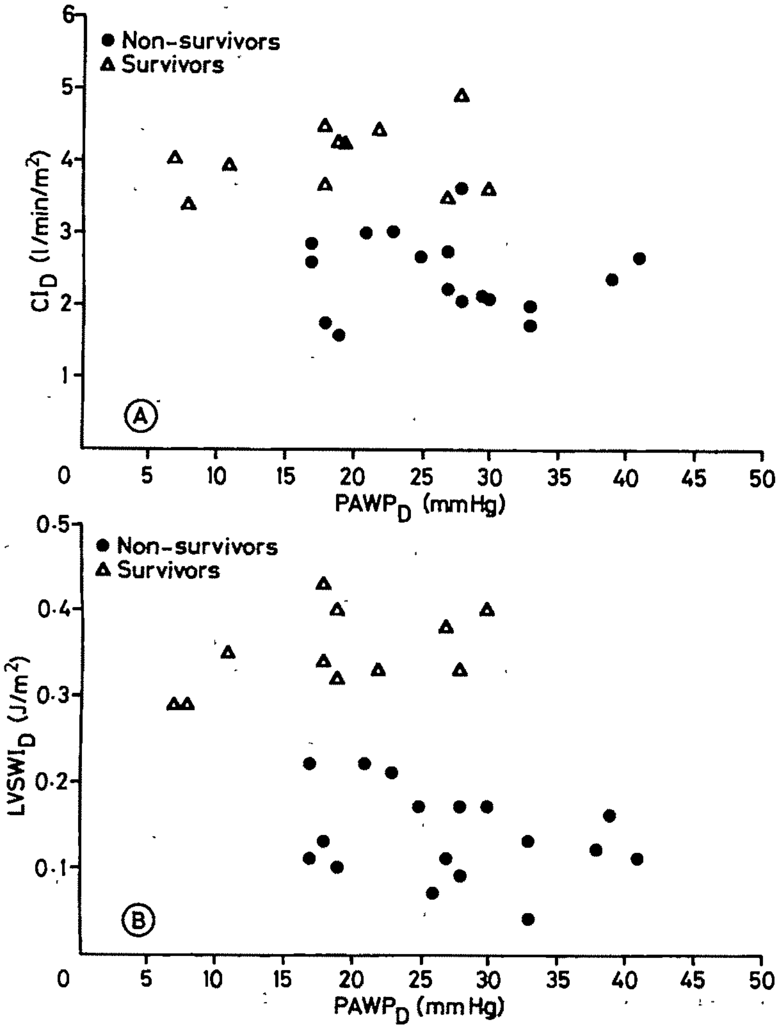


Figure 4 Relation between (A) cardiac index and mean pulmonary artery wedge pressure (PAWP) and (B) left ventricular stroke work index (LVSWI) and pulmonary artery wedge pressure during maximal dobutamine infusion.

in infusion rate tended not to produce concomitant increases in cardiac power output (fig 3B) but the cardiac output continued to increase (fig 3A).

Figure 3A shows that the cardiac index dose-response curves of the two patients (represented by open circles and filled inverted triangles) were similar. However, the cardiac power output dose-responses of the same two patients (fig 3B) were quite different. The patient who died reached a substantially lower peak cardiac power output.

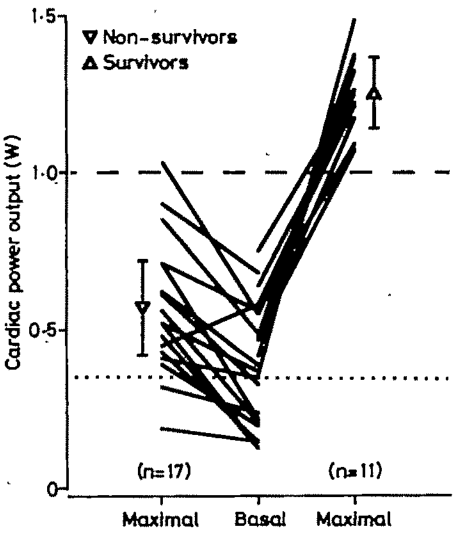


Figure 5 Cardiac power output in basal resting state and during maximal dobutamine stimulation of individual patients (mean and 99% confidence intervals). The cardiac performance of patients with basal cardiac power outputs above 0·35 W (dotted line) is indistinguishable without dobutamine stimulation. This became distinctly different during maximal dobutamine stimulation, with the survivors showing greater cardiac reserve, reaching peak power output of > 1 W (dashed line).

The maximum dose of dobutamine used to determine cardiac reserve in the non-survivor group (25·6 (2·3) μg/kg/min) was significantly higher ($p < 0·05$) than that used in the survivor group (18·2 (1·1) μg/kg/min). Survivors achieved maximal power output at lower rates of dobutamine infusion.

HAEMODYNAMIC STATE AT MAXIMAL INOTROPIC STIMULATION

Table 2 shows that maximal dobutamine stimulation significantly increased, the heart rate, mean arterial pressure, cardiac index, stroke volume index, stroke work index, and cardiac power output of the entire group and significantly decreased the right atrial pressure, pulmonary vascular resistance, and systemic vascular resistance. Pulmonary artery wedge and mean pulmonary arterial pressures did not change significantly in any group in response to dobutamine stimulation. The changes produced by dobutamine were not as statistically significant in the smaller subsets of survivors and non-survivors.

The measured haemodynamic data of survivors and non-survivors at basal resting state were not significantly different (table 2). At peak dobutamine stimulation, however, all variables indicative of systolic cardiac performance (cardiac index, stroke volume index, left ventricular stroke work index, and cardiac power output) in survivors were clearly different from those of non-survivors.

In contrast with figs 2A and B, the relation between cardiac index and pulmonary artery wedge pressure and between left ventricular stroke work index and pulmonary artery wedge pressure during peak dobutamine infusion shown in figs 4A and B were clearly able to identify the subset of non-survivors. Compared with the points in fig 2 the points in fig 4 were generally shifted to the left and upwards by the dobutamine challenge, but this shift was more noticeable in the survivors than in those who died.

PEAK CARDIAC POWER OUTPUT AND PROGNOSIS

Figure 5 shows the individual responses of cardiac power output to dobutamine stimulation. In patients with a basal resting cardiac power output of ≤0·35 W the outcome was uniformly death. Above this level, some had sufficient cardiac reserve to be able to respond to the dobutamine stimulation to produce peak cardiac power output of > 1 W. These patients survived more than a year. The one exception (that is the patient with peak cardiac power output > 1 W who died) was the patient who was discharged home after acute myocardial infarction and was readmitted a month later and died of intractable ventricular tachycardia. Those who had limited cardiac reserve, such that the peak cardiac power output during maximal dobutamine challenge was ≤1 W, died. Also the mean values of peak cardiac power output of survivors and non-survivors, together with the 99% confidence limits (shown as error bars in fig 5), were clearly separate.

Discussion

COMPARISON OF BASAL AND PEAK STIMULATED CARDIAC PUMPING STATES

Haemodynamic evaluation at basal resting state confidently predicted mortality in a group of patients in cardiogenic shock only when the cardiac pump failure was so severe such that resting cardiac index was $<1{\cdot}3$ l.min^{-1}.m^{-1}, left ventricular stroke work index was $<0{\cdot}1$ J.m^{-2} (fig 1), or cardiac power output was $<0{\cdot}35$ W (fig 5). At peak stimulation, however, haemodynamic assessment of the severity of cardiac dysfunction clearly identified which *individual* patient was going to die (figs 4 and 5).

One reason why the predictive value of resting basal cardiac performance is less is because the response to cardiac impairment in patients with cardiogenic shock is not uniform. Different combinations of compensatory neurohormonal responses are activated in different individuals—for example, some patients have a higher vagal tone while others have higher sympathetic tone. Another reason for the poorer predictive value of basal haemodynamic evaluation is that when the heart fails, the peak performance is compromised to a greater extent than the basal performance.[12]

Cardiac pumping capability assessed by pharmacological stimulation has been shown to correlate with that assessed by physiological stimulation via exercise testing.[13] Thus cardiac reserve as estimated by dobutamine challenge can be taken to represent the functional capacity of the failing heart, and hence subsequent exercise capability[12] and prognosis.[9]

RESPONSE TO DOBUTAMINE CHALLENGE

The dose-response curves for dobutamine (figs 3A and B) highlight two related points. First, at the peak dosages further increases in infusion rate tended not to increase the cardiac power output (fig 3B) while the cardiac output continued to rise (fig 3A). The lack of increase in cardiac power output signified the cardiac pump's inability to respond to inotropic stimulation beyond a certain limit. The continued increase in cardiac output, on the other hand, was due to the systemic vasculature remaining responsive to further vasodilatory effects of dobutamine. Second, the relative positions of the four dose-response curves to dobutamine were dissimilar in the two figures (3A and 3B). The patients represented by filled inverse triangles and open circles in fig 3A seemed to have similar cardiac index responses to dobutamine stimulation, but when the cardiac power output of these patients were plotted against the dobutamine dosage (fig 3B) the curves were quite different and were more predictive of the clinical outcome. For these reasons the maximal cardiac response to dobutamine stimulation was determined in our protocol by the peak cardiac power output and not peak cardiac output.

The cardiac index was significantly increased by maximal dobutamine stimulation of the heart (table 2). This increase was not only caused by the significant increase in heart rate but also by the significant increase in stroke volume, which was partly due to the vasodilatation caused by dobutamine, as shown by the decrease in systemic vascular resistance. Because the mean arterial pressure was significantly raised by dobutamine, however, and in the absence of any increase in preload (no rise in pulmonary artery wedge pressure), the increase in stroke volume must have also been the result of the positive inotropic response of the failing hearts to dobutamine.[14] Hence, dobutamine challenge produced enhanced cardiac systolic performance by using the inotropic and chronotropic reserves. This led to significant increases in left ventricular stroke work index and cardiac power output. Also though the basal cardiac power output was marginally lower among those who died, the percentage increase was smaller in this group than among those who survived (67·6% *v* 140·4%, $p < 0{\cdot}01$), indicating a considerable difference in cardiac reserve.

PROGNOSTIC INDICATORS IN CARDIOGENIC SHOCK

Clinical evaluation during cardiogenic shock is imprecise and cannot be relied upon to establish the severity of cardiac dysfunction or prognosis. For example, when they were first diagnosed as being in cardiogenic shock the patients were clinically indistinguishable and were all judged to have grave prognosis by the attending physicians. Nevertheless, the use of clinical acumen to make the diagnosis of cardiogenic shock is invaluable. The detection of oliguria or hypotension by cuff manometry has often been the first feature to alert the clinician to the presence of shock. The finding of a higher intra-arterial pressure in the presence of other clinical features of shock does not preclude the diagnosis of shock, especially in previously hypertensive patients.[10 15] We therefore thought that to study how this new method of haemodynamic evaluation correlated with prognosis, it was more appropriate to base the diagnosis on clinical criteria than on conventional haemodynamic criteria. This may partly account for the higher survival rate (39%) seen in our study as compared with previous published figures of 0–27%,[1] though a figure of 38% was reported more recently.[16]

There were many studies of prognostic indicators in cardiogenic shock in the early 1970s. The management of cardiogenic shock has evolved substantially over the years. With medical treatment all patients with a cardiac index $<2{\cdot}3$ l.min^{-1}.m^{-2} and pulmonary artery wedge pressure of >15 mm Hg died in a series reported in 1972,[7] whereas several such patients survived in our series (fig 2A). Similarly, 93% of patients with stroke work index $<0{\cdot}25$ g.m.m^{-2} died in 1972,[17] but only 63% died in our series. Haemodynamic criteria for diagnosing cardiogenic shock based on evaluation of cardiac function at basal resting states are liable to be either too stringent, so that some true cases of cardiogenic shock are not included, or too lax so that those with reasonable prognosis are given unnecessary treatment.

The outcome of patients in cardiogenic shock may depend on the progression of the underlying disease as well as on cardiac pumping reserve; and further deterioration, such as caused by ischaemia/infarction, is likely to contribute significantly towards further setbacks and mortality. However, our results showed that cardiac reserve, estimated soon after the onset of cardiogenic shock, correlated closely with the outcome during the one year of follow up. This implies that progression of coronary artery disease, in this population group, affects medium term prognosis only slightly, if at all. Another recent study also showed that, in patients in cardiogenic shock, the death rate in the first year after hospital discharge was low (only 4%, <1/10 of in-hospital mortality).[18] A possible explanation of this is that by the time the patient reached the state of shock the damage to the jeopardised myocardium was probably complete, and, if not, then the shock state itself would ensure that any threatened myocardium was progressively infarcted.[19 20] This does not, however, preclude the possibility that further infarction and rhythm disturbances affect mortality in the longer term.

Figures 4A and B show that the response to peak dobutamine stimulation distinguished the survivors from those who died. As pointed out above, a variable representing both the pressure and flow generating capacity of the failing heart, such as left ventricular stroke work index, gave a better separation of the data points of survivors from the non-survivors (fig 4B) than one measuring flow alone (fig 4A). The cardiac index-pulmonary wedge pressure criteria for identifying the groups with a poor prognosis, obtained during maximal dobutamine challenge, can now be defined as a cardiac index of <3.1 $l.min^{-1}.m^{-2}$ and pulmonary artery wedge pressure of >17 mm Hg (fig 4A); the left ventricular stroke work index-pulmonary wedge pressure criteria are a stroke work index of <0.25 J/m^2 and a pulmonary artery wedge pressure of >17 mm Hg (fig 4B).

PEAK CARDIAC POWER OUTPUT AND PROGNOSIS

Although the separation of the survivors from the non-survivors in fig 4B is apparent, it does not explain why the survivors managed to do well despite the fact that the left ventricular stroke work index at peak dobutamine stimulation (mean of 0·35 J/m^{-2}, see table 2) was still significantly below the stroke work index of a healthy comparison group at rest without stimulation (mean of 0·52 J/m^2).[21] One explanation is that the term, peak stroke work index, contains two of the three major components of cardiac reserve—that is, preload and contractility, leaving out heart rate. In the face of impaired contractility and maximal use of preload, the heart is highly dependent on its chronotropic competence to maintain adequate circulation.[22]

The inclusion of heart rate in stroke work leads to the term cardiac power output, which has been previously described as the entity solely responsible for the maintenance of the circulation.[9] Survival was limited when the peak cardiac power output during maximal stimulation fell short of the normal value of the basal unstimulated state.[9] Ideally, the normal basal cardiac power output of the individual patient should be compared with the value before the development of heart disease; but this is seldom known. The basal resting cardiac power output of an adult of average size (approximately 1 W) was used instead.[9] The results of this study (fig 5) accord with the supposition that if the function of the failing heart performing at its maximal capacity (peak cardiac power output) does not exceed that which is normally required during inactivity (cardiac power output of approximately 1 W) then such a heart cannot be expected to sustain life for long. Conversely, when peak cardiac power output exceeds the normal basal cardiac power output, then, despite the peak left ventricular stroke work index being significantly below the normal basal stroke work index, the function of the failing heart would still be compatible with sustained survival.

IMPLICATIONS FOR MANAGEMENT AND FUTURE RESEARCH

Our results showed that patients with adequate cardiac reserve who were treated medically survived for more than a year. Should such patients have acute interventions, such as the insertion of ventricular assist devices, emergency coronary angioplasty, or coronary bypass surgery?[23] These interventions are not without morbidity and mortality[24 25] and their long term benefits are uncertain. A recent report suggests that coronary angioplasty improves the survival of patients in cardiogenic shock after infarction.[26] However, the study had the shortcoming of being a retrospective unrandomised study with permissive criteria for patient selection (shock precipitated by drugs, arrhythmia, or heart block was not expressly excluded). Survival at 30 days was 50% in the angioplasty group and 17% in the medically treated group, but the angioplasty group was recruited between 1983 and 1985 and the medically treated group between 1975 and 1985. Our patients with cardiogenic shock were treated conservatively and in the same study period as the angioplasty group; their 30 day survival was 46%. Prospective randomised trials in carefully selected patients are needed to establish the cost/benefit ratio of immediate and invasive interventions.

Randomisation of cardiogenic shock patients to evaluate the merits of different treatments has been regarded as ethically unacceptable.[27] But randomisation of an objectively selected group of patients in cardiogenic shock who all have a grave prognosis is justifiable. It would also obviate such questions as whether intra-aortic balloon counterpulsation should be started before or after a trial of maximal medical treatment (different institutions have different policies—for example, Pasternak and Braunwald's group recommends intra-aortic balloon counterpulsation when medical treatment fails,[28] whereas Gunnar's group recommends intra-aortic balloon counterpulsation immediately.[29] From our results, it is clear that the group with a poor prognosis should have intra-aortic balloon counterpulsation, whereas the group with a good prognosis should first be given inotropic support. This decision can be made early after the onset of cardiogenic shock, and does not have to wait until the patient becomes unresponsive to medical treatment.[27] Future efforts should thus concentrate on the group with poor prognosis defined above. Those in whom surgery is clearly indicated should receive intervention at the appropriate time. Some patients may have a stunned myocardium[30,31] and it is unclear whether inotropic support and the use of ventricular assist devices for a prolonged period would allow the stunned myocardium to recover sufficiently to avoid the need for cardiac transplantation. On the other hand, those patients in cardiogenic shock whose condition is identified to be truly terminal, and who (for whatever reasons) are not candidates for surgery, should not be put through frantic therapeutic manoeuvres that may postpone death but in so doing prolong suffering.[32]

PRACTICAL GUIDELINES

Our method can be simplified for use at the bedside. Once relative hypovolaemia and rhythm and conduction disturbances have been corrected in a patient in cardiogenic shock a basal cardiac index of $< 1{\cdot}3$ l.min^{-1}.m^{-2}, left ventricular stroke work index of $< 0{\cdot}1$ J.m^{-2}, or cardiac power output of $< 0{\cdot}35$ W identifies those with a grave prognosis. The dobutamine challenge test should be used in patients with higher values than these to see whether the maximal cardiac power output is $< 1{\cdot}0$ W and left ventricular stroke work index is $< 0{\cdot}25$ J/m^2; this too indicates a poor prognosis. In patients with a poor prognosis, medical treatment would be futile, and unless contraindicated, the patient will need intra-aortic balloon counterpulsation or other ventricular assist devices to sustain them until coronary recanalisation or transplantation.

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1 Ayres SM. The prevention and treatment of shock in acute myocardial infarction. *Chest* 1988;93(suppl):17S–21S
2 Wanzer SH, Federman DD, Adelstein SJ, *et al*. The physician's responsibility toward hopelessly ill patients: a second look. *N Engl J Med* 1989;320:844–9.
3 Hill JD, Farrar DJ, Hershon JJ, *et al*. Use of prosthetic ventricle as a bridge to cardiac transplantation for post-infarction cardiogenic shock. *N Engl J Med* 1986;314 626–8
4 Farrar DJ, Hill JD, Gray LA, *et al*. Heterotopic prosthetic ventricles as a bridge to cardiac transplantation A multicenter study in 29 patients *N Engl J Med* 1988;318: 333–40.
5 Mulcahy D, Wright C, Mockus L, Yacoub M, Fox K. Cardiac transplantation in severely ill patients requiring intensive support in hospital. *BMJ* 1988;296:817–9.
6 Resnekov L. Cardiogenic shock. *Chest* 1983,6:893–8.
7 Ratshin RA, Rackley CE, Russell RO. Hemodynamic evaluation of left ventricular function in shock complicating myocardial infarction. *Circulation* 1972;45:127–39.
8 Russell RO Jr, Rackley CE, Pombo J, Hunt D, Potanin C, Dodge HT Effects of left ventricular filling pressure with acute myocardial infarction *J Clin Invest* 1970;49: 1539–50
9 Tan LB. Cardiac pumping capability and prognosis in heart failure. *Lancet* 1986,ii:1360–3.
10 Cohn JN. Recognition and management of shock and acute pump failure. In: Hurst JW, ed. *The heart*. 5th ed. New York: McGraw-Hill, 1982:463–76.
11 Vincent J-L, Weil MH, Puri V, Carlson RW. Circulatory shock associated with purulent peritonitis *Am J Surg* 1981;142:262–70.
12 Tan LB. Clinical and research implications of new concepts in the assessment of cardiac pumping performance in heart failure *Cardiovasc Res* 1987,21:615–22.
13 Tan LB, Bain RJI, Littler WA. Assessing cardiac pumping capability by exercise testing and inotropic stimulation. *Br Heart J* 1989;62:20–5.
14 Tan LB, Murray RG, Littler WA. An analytical method to separate inotropic and vasodilatory drug effects in man. *Cardiovasc Res* 1987;21:625–30.
15 Strobeck JE. Cardiogenic shock. *Heart Failure* 1985;1: 13–35.
16 Vincent J-L, Carlier E, Berre J, *et al* Administration of enoximone in cardiogenic shock *Am J Cardiol* 1988;62· 419–23.
17 Prakash R, Forrester J, Parmley WW, Swan HJC. Prognostic implications of left ventricular stroke work index (SWI) in acute myocardial infarction [Abstract]. *Clin Res* 1972;20:391.
18 Stack RS, Califf RM, Hinohara T, *et al*. Survival and cardiac event rates in the first year after emergency coronary angioplasty for acute myocardial infarction. *J Am Coll Cardiol* 1988,11·1141–9.
19 Hands ME, Rutherford JD, Muller JE, *et al*. The in-hospital development of cardiogenic shock after myocardial infarction: incidence, predictors of occurrence, outcome and prognostic factors. *J Am Coll Cardiol* 1989,14.40–6.
20 Gutovitz AL, Sobel BE, Roberts R Progressive nature of myocardial injury in selected patients with cardiogenic shock. *Am J Cardiol* 1978;41:469–75.
21 Grossman W. Evaluation of systolic and diastolic function of the myocardium. In: Grossman W, ed. *Cardiac catheterization and angiography*, 3rd ed. Philadelphia: Lea and Febiger, 1986:301–19.
22 Colucci WS, Ribeiro JP, Rocco MB, *et al*. Impaired chronotropic response to exercise in patients with congestive heart failure. Role of postsynaptic β-adrenergic desensitization *Circulation* 1989,80:314–23.
23 Mathey D, Kuck KH, Remmecke J, Tilsner V, Bleifeld W. Transluminal recanalization of coronary artery thrombosis: a preliminary report of its application in cardiogenic shock. *Eur Heart J* 1980;1:207–12.
24 Isner JM, Cohen SR, Virmani R, Lawrinson W, Roberts WC. Complications of the intra-aortic balloon counterpulsation device. clinical and morphologic observations in 45 necropsy patients. *Am J Cardiol* 1980;45·260–8.
25 McCabe JC, Abel RM, Subramaniam VA, Gay WA Jr. Complications of intra-aortic balloon insertion and counterpulsation. *Circulation* 1978;57:769–73.
26 Lee L, Bates ER, Pitt B, Walton JA, Laufer N, O'Neill WW. Percutaneous transluminal coronary angioplasty improves survival in acute myocardial infarction complicated by cardiogenic shock. *Circulation* 1988;78:1345–51.
27 Moulopoulos S, Stamatelopoulos S, Petrou P. Intra-aortic balloon assistance in intractable cardiogenic shock. *Eur Heart J* 1986;7:396–403.
28 Pasternak RC, Braunwald E, Sobel BE. Acute myocardial infarction. In. Braunwald E, ed. *Heart disease*. Philadelphia: WB Saunders, 1988:1279–1313.
29 Gunnar RM, Loeb HS. Shock in acute myocardial infarction evolution of physiologic therapy. *J Am Coll Cardiol* 1983,1:154–63.
30 Braunwald E, Kloner RA. The stunned myocardium: prolonged postischemic ventricular dysfunction. *Circulation* 1982;66:1146–9.
31 Ballantyne CM, Verani MS, Short HD, Hyatt G, Noon GP Delayed recovery of severely "stunned" myocardium with the support of a left ventricular assist device after coronary bypass graft surgery. *J Am Coll Cardiol* 1987;10·710–2.
32 Ruark JE, Raffin TA, and the Stanford University Medical Center Committee on Ethics. Initiating and withdrawing life support. Principles and practice in adult medicine *N Engl J Med* 1988;318:25–30.

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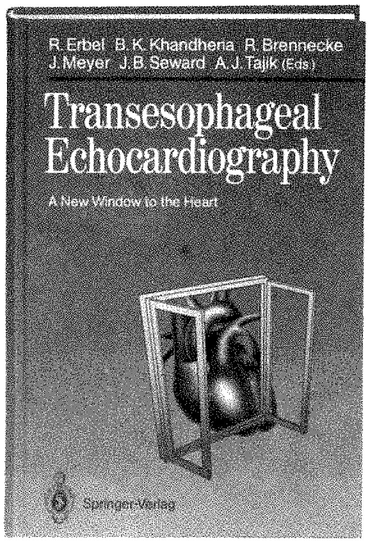
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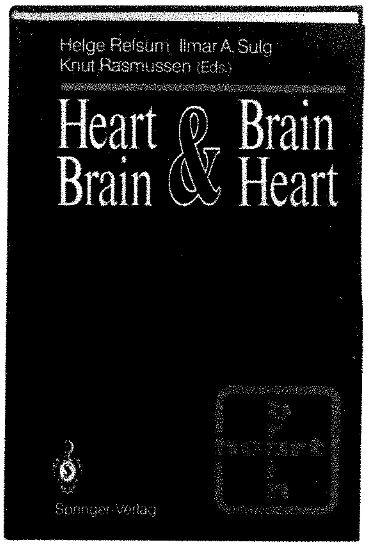

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Acute effects of ethanol on left ventricular diastolic function

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Abstract

Transmitral flow velocities were measured by Doppler echocardiography in nine healthy men who ingested 1 g/kg of ethanol within one hour. The measurements were made before the first drink and every hour thereafter for three hours. The peak mean (SE) blood ethanol concentration was 21·4 (1·0) mmol/l. Each man was also studied after drinking fruit juice. Ethanol increased the heart rate but did not change the peak transmitral velocities, the normalised peak filling rate, the deceleration of early flow, or the duration of relaxation as measured from the second heart sound to the peak early diastolic velocity. The ratio of the peak atrial to the peak early diastolic velocity rose from 0·41 (0·03) to 0·44 (0·03) after ethanol but remained unchanged after juice. The difference between juice and ethanol was independent of changes in heart rate. The fluid balance was more negative in the ethanol experiment (−727 (114) ml *v* −107 (70) ml), suggesting a reduction in preload, and the ethanol-induced net loss of fluid correlated with the concomitant change in the velocity ratio.

A moderate dose of ethanol causes a small acute increase of the ratio of the peak atrial to the peak early diastolic velocity of mitral flow in healthy subjects. Although this change indicates altered diastolic function of the left ventricle, most of it may result from the diuretic effect of ethanol. Any major impairment of ventricular relaxation seems unlikely.

Even a moderate dose of alcohol can change left ventricular systolic performance through its effects on contractility, heart rate, and loading conditions.[1–3] Its effects on diastolic function are less certain. In theory, ventricular relaxation could be compromised because alcohol can inhibit calcium cycling in the myocardial cell, at least at high concentrations.[4 5] We therefore used Doppler ultrasound to examine the effects of a moderate dose of ethanol on the transmitral blood flow velocities in healthy men. The Doppler method has been shown to be sensitive both to acute and chronic alterations in ventricular diastolic performance.[6 7]

Subjects and methods

SUBJECTS AND STUDY DESIGN

The study group consisted of nine male volunteers aged 23 to 28 years. All were healthy—as shown by a clinical examination, a 12 lead electrocardiogram, and cross sectional echocardiography. They used alcohol only in moderation: the reported average consumption ranged from 5 to 35 g of ethanol/day (median 11 g/day).

The men entered the cardiovascular laboratory at 3:00 pm having fasted for 6 hours before the study. They emptied their bladders, and an indwelling cannula was inserted into an antecubital vein for blood sampling. Baseline recordings of arterial blood pressure (automated oscillometry), Doppler transmitral flow velocities, and M mode echocardiograms of the left atrium and left ventricle were made after a 30 minute supine rest. Thereafter the men ingested ethanol 1 g/kg as a 15% (w/v) dilution in juice within one hour. The measurements described above were repeated every hour up to three hours after they started to drink. The volume of urine excreted during the study was measured and subtracted from the volume of fluid ingested. This gave the net loss of fluid (excluding evaporation and perspiration). Each man also took part in a control experiment in which the ethanol was replaced by the same volume of juice; the order of experiments was randomised. Samples of venous blood were taken to measure the blood ethanol concentration[8] before ethanol or juice ingestion and 20, 40, 60, 80, 100, 120, and 180 minutes after the first ethanol drink.

M MODE AND DOPPLER ECHOCARDIOGRAPHY

We used a Toshiba SSH-60A echocardiograph equipped with a 3·7 MHz phased array transducer and a strip chart recorder for the cross sectional and M mode echocardiographic studies. The M mode recordings of the left ventricle and left atrium were taken through the sector scan by methods described in detail elsewhere.[9]

The pulsed Doppler recordings of the transmitral flow were made with a Toshiba SDS-60A Doppler unit (incorporated into the SSH-60A scanner) and a 2·5 MHz transducer. This system analyses the Doppler shifts by a fast Fourier transform and displays the velocity spectra every 5 ms in real time. All studies were made with the man lying in the left lateral position and from an apical transducer position. With cross sectional guidance we placed the sample volume between the mitral valve leaflets just distal to the mitral annulus, with the ultrasound beam directed in parallel with the assumed left ventricular inflow. The position and size of the sample volume were thereafter adjusted according to the Doppler signal to obtain maximal and clearly defined velocity waveforms. No angle correction was applied. The velocity spectra were recorded during quiet respiration together with an electrocardiogram and an external phonocardiogram at a paper speed of 50 m/s.

M mode and Doppler recordings were coded and analysed blindly with a tablet digitiser and computer assistance. The left ventricular end diastolic diameter and the left atrial diameter were measured according to the European standardisation.[10] The midpoints of the darkest portions of the Doppler velocity waveforms were traced on the digitising tablet and the computer automatically calculated the peak late (atrial) and early diastolic velocities, their arithmetic ratio, and the ratio of the peak early diastolic velocity to the total time velocity integral—that is the normalised peak filling rate according to Bowman *et al.*[11] The relaxation time was measured from the beginning of the second heart sound on the phonocardiogram to the point of the peak early diastolic velocity; this time covers the period of relaxation more completely rather than merely the duration of isometric relaxation.[12] We determined the deceleration of the early flow by fitting a straight line to the first half of the down slope of the early velocity wave. All measurements were the average of five cardiac cycles.

REPRODUCIBILITY

In five healthy men aged 32 to 42 years we recorded transmitral flow velocities twice under identical conditions at an interval of one hour. As in our ethanol study, the first recording was preceded by a 30 minute rest and the men lay supine between the recordings. The reproducibility of the Doppler measurements was assessed by the method of Bland and Altman[13] by taking square roots of the mean square differences between the two examinations. These (that is, the standard deviations of the differences) were as follows: 4·5 cm/s for the peak early velocity, 3·8 cm/s for the peak late velocity, 0·05 for the late to early peak velocity ratio, 64 cm/s^2 for the deceleration of flow, 10 ms for the relaxation time, and 0·4/s for the normalised peak filling rate. These figures compare well with the reproducibility data reported recently by Fast *et al* and Spirito *et al.*[14,15] The reproducibility of our M mode echocardiographic technique has been reported earlier.[9]

STATISTICAL ANALYSIS

We used methods available in the BMDP statistical software. Because the men served as their own controls, repeated measurements analysis of variance and covariance with no grouping factor and time and treatment as within factors were used to compare the effects of ethanol and juice on the cardiovascular measurements (BMDP 2V).[16] Heart rate was used as a covariate that changed over all levels of the within factors to adjust for the rate dependency of the Doppler velocity measurements.[17] In analysing changes in the late to early peak velocity ratio we used the net loss of fluid during the experiment as a second covariate (changing over the levels of treatment) to adjust for the preload sensitivity of this measurement.[17] We used the least squares method for correlation analysis. We used a paired *t* test to compare the fluid balance between the ethanol and juice experiments. All tests were two tailed; p values <0·05 were regarded as statistically significant. The data are given as mean (SE).

Results

BLOOD ETHANOL

The blood ethanol concentration was <0·6 mmol/l in each man before both ethanol and juice ingestion. After ethanol intake blood ethanol measured 16·5 (0·8) mmol/l at the completion of the drinking period, 21·0 (1·0) mmol/l 40 minutes later, and 18·3 (1·0) mmol/l at the end of the experiment. The fluid balance was −727 (114) ml after ethanol and −107 (70) ml after juice (p < 0·001).

CARDIOVASCULAR MEASUREMENTS

Table 1 summarises the data on heart rate,

Table 1 Heart rate, blood pressure, left ventricular end diastolic diameter, and left atrial diameter (mean (SEM)) before and after ingestion of ethanol (1 g/kg within one hour) or an equal volume of juice

		Time (h) after drinking started				*F values**		
Measurement		*0*	*1*	*2*	*3*	*Treatment*	*Time*	*Treatment × time interaction*
Heart rate (beats/min)	J	55 (2)	52 (2)	54 (2)	51 (2)	8·8†	0·5	7·9‡
	E	52 (2)	56 (2)	56 (3)	56 (2)			
Systolic blood pressure (mm Hg)	J	106 (4)	109 (3)	110 (2)	111 (3)	0·2	1·4	0·8
	E	107 (3)	111 (3)	108 (3)	108 (3)			
Diastolic blood pressure (mm Hg)	J	63 (2)	64 (1)	65 (2)	67 (2)	4·3	1·3	0·5
	E	62 (3)	62 (3)	60 (3)	63 (2)			
LV end diastolic diameter (mm)	J	51·7 (0·8)	51·6 (0·7)	51·5 (0·5)	51·1 (0·7)	0·2	3·7†	1·0
	E	52·0 (0·6)	51·8 (0·7)	50·7 (0·7)	50·5 (0·7)			
Left atrial diameter (mm)	J	34·8 (1·5)	35·3 (1·4)	33·6 (1·4)	32·8 (1·4)	0·1	17·5§	0·5
	E	34·6 (1·3)	35·1 (1·4)	33·8 (1·0)	31·8 (1·1)			

*F values from repeated measurements analysis of variance; the degrees of freedom are 1, 8 for the treatment effect and 3, 24 for the effects of time and the treatment × time interaction. †p < 0·05; ‡p < 0·01; §p < 0·001. E, ethanol; J, juice; LV, left ventricular.

Table 2 Doppler velocimetry of mitral flow before and after ingestion of ethanol (1 g/kg within one hour) or an equal volume of juice (mean (SEM))

		Time (h) after drinking started				*F values**			
Measurement		*0*	*1*	*2*	*3*	*Treatment*	*Time*	*Treatment × time interaction*	*Heart rate*
Peak atrial velocity (cm/s)	J	24 (2)	23 (2)	22 (1)	22 (2)	4·9	1·9	0·4	9·4†
	E	24 (1)	26 (2)	25 (2)	24 (1)				
Peak early diastolic velocity (cm/s)	J	61 (3)	60 (4)	58 (4)	57 (3)	0·1	4·0†	2·9	0·0
	E	61 (4)	62 (4)	59 (4)	59 (4)				
Atrial to early peak velocity ratio	J	0·39 (0·03)	0·40 (0·03)	0·39 (0·03)	0·39 (0·04)	10·6†	0·2	1·1	6·9
	E	0·41 (0·03)	0·44 (0·04)	0·44 (0·03)	0·43 (0·04)				
Deceleration of early flow (cm/s^2)	J	420 (33)	428 (57)	370 (28)	375 (27)	0·0	2·0	0·7	0·3
	E	426 (40)	450 (40)	414 (42)	418 (40)				
Peak normalised filling rate (s^{-1})	J	4·1 (0·1)	4·1 (0·1)	4·2 (0·1)	4·1 (0·2)	0·4	1·7	0·7	7·8†
	E	4·2 (0·1)	4·5 (0·2)	4·2 (0·1)	4·4 (0·1)				
Relaxation time (ms)	J	196 (8)	190 (6)	193 (6)	194 (6)	0·0	1·6	1·3	6·8†
	E	207 (9)	196 (6)	196 (6)	196 (4)				

*F values from repeated measurements analysis of covariance with heart rate as a changing covariate; the degrees of freedom are 1, 7 for the effects of treatment and heart rate and 3, 23 for the effect of time and for the treatment × time interaction. †$p < 0·05$. E, ethanol; J, juice.

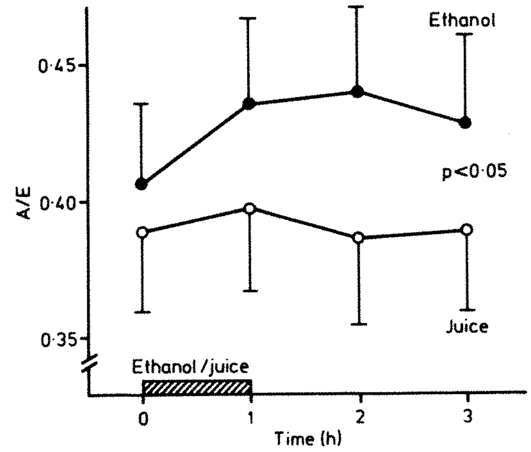
blood pressure, and left ventricular and atrial diameters. The results of the analyses of variance are also given. Compared with juice, ethanol increased heart rate ($p = 0·018$ for the treatment effect and $p = 0·001$ for the treatment × time interaction) but did not give a statistically significant change in either systolic or diastolic blood pressure or the diameters of the left ventricle or the left atrium.

Table 2 summarises the Doppler velocity measurements and the results of the repeated measurements analyses of covariance. A statistically significant treatment effect (that is, an effect of ethanol independent of the effects of time and heart rate) was found only in the ratio of late to early peak velocity, which rose from 0·41 (0·03) to 0·44 (0·03) 2 hours after ethanol but was unchanged 2 hours after juice ($p = 0·014$) (figure). There was a modest direct correlation ($r = 0·50$) between the net loss of fluid and the change in the peak velocity ratio from the baseline to the 3 hour recording in the ethanol study, suggesting that the larger the diuresis the more prominent was the rise in the peak velocity ratio. When the net loss of fluid was included as a second covariate in the analysis the treatment effect on the velocity ratio became non-significant ($F = 1·22$, $p = 0·312$).

Discussion

The study of left ventricular diastolic function by Doppler echocardiography is based on measuring the velocity of blood flow through the mitral valve during ventricular filling. This technique has rapidly gained in popularity because it is non-invasive, simple, and repeatable. Velocity derived indices of ventricular filling correlate with both cineangiographic[18] and radionuclide angiographic[11] data, and simultaneous catheterisation and Doppler studies have shown that the method can expose both relaxation and compliance abnormalities of the left ventricle.[19] A limitation of this technique is that in addition to diseases and therapeutic interventions factors such as age, heart rate, loading conditions, and left atrial pressure can also influence the transmitral velocities.[7 17] In our study, both heart rate and time seemed to have significant effects (see table 2). Although the effect of time, a novel finding, may simply be a reflection of the present experimental conditions, it could as well indicate diurnal variation in diastolic function and therefore deserves further study.

Analysis and interpretation of the Doppler data for differences or changes in the intrinsic ventricular diastolic properties must take into account the contribution of the confounding factors such as time and heart rate. When groups of patients are studied this can be done in part by proper use of statistical techniques. We have found methods of covariance analysis very useful in this respect, both in cross sectional between-group comparisons and, as the present work shows, in studying serial changes in diastolic function. These techniques do not solve the problem of interpreting individual data, however, which probably need nomograms adjusted for age and heart rate at least.



Ratio of atrial to early peak velocity (A/E) in nine healthy men before and after ingestion of 1 g/kg of ethanol or the same volume of juice.

ETHANOL AND DIASTOLIC FUNCTION

We found that ethanol induced a small increase in the ratio of late to early peak velocity. An increase in heart rate,[20] a reduction in preload,[21] or an impairment of relaxation[19] could produce this. We think that a reduction in preload was the most likely mechanism in our study because the change was rate independent, there were no differences in the relaxation time or in the deceleration of flow, and the change in the velocity ratio correlated with the amount of fluid loss that ethanol provoked. This interpretation accords with the results of covariance analysis in which the treatment effect was adjusted for the fluid loss, and it also accords with previous reports showing that ethanol reduced preload in healthy people[1 2 22] and in patients with congestive heart failure.[23] As in our earlier study,[2] we found bigger reductions in the sizes of the left ventricle and atrium after ethanol than after juice, indicating that ethanol affected the preload (but not significantly). A reduction in preload changes the velocity ratio by decreasing the peak early velocity or, in addition, by increasing peak late velocity.[21 24] In our study the rise in the velocity ratio was apparently mainly the result of a change in the atrial component, though again the effect of ethanol on the peak atrial velocity did not quite reach statistical significance (F = 4·9, p = 0·06; see table 2).

Both experimental and clinical studies suggest that prolonged and heavy use of alcohol can impair left ventricular filling before or concomitantly with contractile deterioration. In a canine model of chronic alcoholism, the first myocardial abnormality to appear was a decrease in left ventricular compliance,[25] and in alcoholic patients left ventricular end diastolic pressure may be increased despite a normal or even a decreased end diastolic volume.[26] Recently, Silberbauer *et al* reported the results of Doppler velocimetry in alcoholic patients who were free of clinically evident heart disease.[27] Compared with healthy controls, alcoholic patients showed changes in the peak velocity ratio and in the isovolumetric relaxation time indicative of impaired relaxation despite normal left ventricular mass and systolic performance. Although chronic heavy drinking seems to impair left ventricular diastolic function, our data suggest that a single modest dose of alcohol does not produce comparable adverse effects in healthy men.

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1 Lang RM, Borow KM, Neumann A, Feldman T. Adverse cardiac effects of acute alcohol ingestion in young adults. *Ann Intern Med* 1985;**102**:742–7.

2 Kupari M. Acute cardiovascular effects of ethanol: a controlled non-invasive study. *Br Heart J* 1983;**49**:174–82.

3 Kelbaek H, Gjorup T, Brynjolf I, Christensen NJ, Godtfredsen J. Acute effects of alcohol on left ventricular function in healthy subjects at rest and during upright exercise. *Am J Cardiol* 1985;**55**:164–7.

4 Gvozdjak A, Kruty F, Bada V, Niederland TE, Gvozdjak J. The effects of ethanol on myocardial mitochondrial and sarcoplasmic ATPase in rats. *Cor Vasa* 1977;**19**:237–42.

5 Swartz M, Repke DI, Katz AM, Rubin E. Effects of ethanol on calcium binding and uptake by cardiac microsomes. *Biochem Pharmacol* 1974;**23**:2369–76.

6 Wind BE, Snider AR, Buda AJ, O'Neill WW, Topol EJ, Dilworth LR. Pulsed Doppler assessment of left ventricular diastolic filling in coronary artery disease before and immediately after coronary angioplasty. *Am J Cardiol* 1987;**59**:1041–6.

7 Spirito P, Maron BJ. Doppler echocardiography for assessing left ventricular diastolic function. *Ann Intern Med* 1988;**109**:122–6.

8 Eriksson CJP, Sippel HW, Forsander OA. The determination of acetaldehyde in biological samples by head-space gas chromatography. *Anal Biochem* 1977;**80**:116–24.

9 Kupari M. Reproducibility of M-mode echocardiographic assessment of left ventricular function. Significance of the temporal range of measurements. *Eur Heart J* 1984;**5**:412–8.

10 Roelandt J, Gibson DG. Recommendations for the standardization of measurements for M-mode echocardiograms. *Eur Heart J* 1980;**1**:375–8.

11 Bowman LK, Lee FA, Jaffe CC, Mattera J, Wackers FJT, Zaret BL. Peak filling rate normalized to mitral stroke volume: a new Doppler echocardiographic filling index validated by radionuclide angiographic techniques. *J Am Coll Cardiol* 1988;**12**:937–43.

12 Nishimura RA, Housmans PR, Hatle LK, Tajik AJ. Assessment of diastolic function of the heart: background and current applications of Doppler echocardiography. Part I. Physiologic and pathophysiologic features. *Mayo Clin Proc* 1989;**64**:71–81.

13 Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet* 1986;**i**:307–10.

14 Fast J, van Dam I, Heringa A, *et al.* Limits of reproducibility of mitral pulsed Doppler spectra. *Am J Cardiol* 1988;**61**:891–4.

15 Spirito P, Maron BJ, Verter I, Merrill JS. Reproducibility of Doppler echocardiographic measurements of left ventricular diastolic function. *Eur Heart J* 1988;**9**:879–86.

16 Jennrich R, Sampson P, Frane J. Analysis of variance and covariance including repeated measures. In: Dixon WS, Brown MB, Engelman L, *et al. BMDP statistical software.* Berkeley, California: University of California Press, 1985:359–87.

17 Nishimura RA, Housmans PR, Hatle LK, Tajik AJ. Assessment of diastolic function of the heart: background and current applications of Doppler echocardiography. Part II. Clinical studies. *Mayo Clin Proc* 1989;**64**:181–204.

18 Ferguson JJ, Manning WJ, Come PC. Pulsed Doppler echocardiographic determination of the time course of left ventricular filling: validation with cineangiography. *Am Heart J* 1989;**117**:127–32.

19 Appleton CP, Hatle LK, Popp RL. Relation of transmitral flow velocity patterns to left ventricular diastolic function: new insights from a combined hemodynamic and Doppler echocardiographic study. *J Am Coll Cardiol* 1988;**12**:426–40.

20 Smith SA, Stoner JE, Russell AE, Sheppard JM, Aylward PE. Transmitral velocities measured by pulsed Doppler in healthy volunteers: effects of acute changes in blood pressure and heart rate. *Br Heart J* 1989;**61**:344–7.

21 Choong CY, Herrman HC, Weyman AE, Fifer MA. Preload dependence of Doppler-derived indexes of left ventricular diastolic function in humans. *J Am Coll Cardiol* 1987;**10**:800–8.

22 Koskinen P, Kupari M, Nieminen MS, *et al.* Effects of alcohol on systemic and pulmonary hemodynamics in normal humans. *Clin Cardiol* 1986;**9**:479–82.

23 Greenberg BH, Shutz R, Grunkemeier GL, Griswold H. Acute effects of alcohol in patients with congestive heart failure. *Ann Intern Med* 1982;**97**:171–5.

24 Bhatia SJS, Theard MA, Plappert T, St John Sutton MG. Effects of altered loading conditions on transmitral Doppler blood flow velocity [Abstract]. *Circulation* 1987;**76** (suppl IV):124.

25 Thomas G, Haider B, Oldewurtel HA, Lyons MM, Yeh CK, Regan TJ. Progression of myocardial abnormalities in experimental alcoholism. *Am J Cardiol* 1980;**46**:233–41.

26 Ahmed SS, Levinson GE, Fiore JJ, Regan TJ. Spectrum of heart muscle abnormalities related to alcoholism. *Clin Cardiol* 1980;**3**:335–41.

27 Silberbauer K, Juhasz M, Ohrenberger G, Hess C. Noninvasive assessment of left ventricular diastolic function by pulsed Doppler echocardiography in young alcoholics. *Cardiology* 1988;**75**:431–9.

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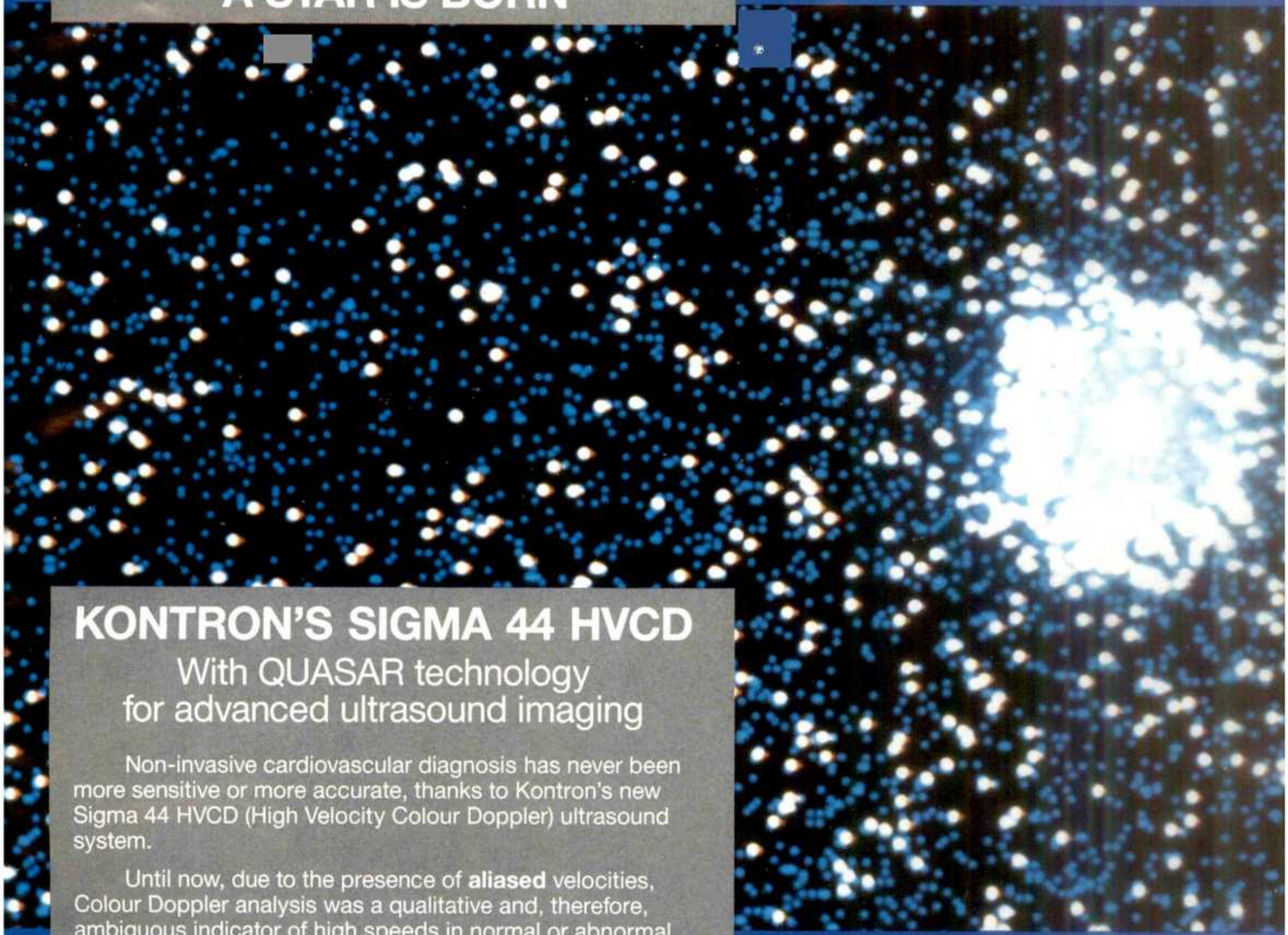

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Continuous wave Doppler echocardiography and coarctation of the aorta: gradients and flow patterns in the assessment of severity

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Abstract

Indices of the severity of coarctation derived from non-invasive Doppler echocardiography were compared with measurements derived from cardiac catheterisation and angiography. In 24 Doppler studies from 17 children instantaneous peak systolic and diastolic gradients and time to half peak systolic and diastolic velocities were compared with the ratio of the coarctation diameter to the diameter of descending aorta at the level of diaphragm obtained from angiographic systolic frames of the aorta. A high peak systolic gradient (>40 mm Hg) or long time to half peak diastolic velocity (>100 ms) (that is, maintenance of flow in diastole) were both highly specific (100%) in detecting coarctation of the aorta where the angiographic ratio was ≤0·5. Diastolic measurements, however, were more sensitive (79% both for peak diastolic gradient and for time to half peak diastolic velocity) than systolic (57% for peak systolic gradient and 64% for time to half peak systolic velocity). Even higher sensitivity (93%) was obtained when the peak systolic gradient was > 40 mm Hg or the time to half peak diastolic velocity was >100 ms.

Examination by continuous wave Doppler echocardiography is an effective non-invasive method of assessing the severity of coarctation of the aorta, particularly when systolic and diastolic events are considered together. This approach overcomes the relatively low sensitivity of peak systolic gradient alone.

Clinical presentation of coarctation of the aorta varies with the age of the patient and the severity of coarctation. In the neonatal period, heart failure may be precipitated by closure of the ductus arteriosus, blood flow to the lower body having been dependent on ductal patency. Older children are usually symptom free. Non-palpable or weak femoral pulses with normal or increased pulses in the arm are the most specific findings that lead to the diagnosis, but these useful clinical findings may be absent. In the neonatal period there may be a large ductus and in older children an extensive collateral circulation may result in normal femoral pulses. Blood pressure measurements in the arms and legs and gradients measured across the coarctation area by Doppler echocardiography can give some indication of severity. Differences in pressures, however, depend not only on the severity of the coarctation but also on flow from collaterals and on cardiac output.

Instantaneous peak systolic gradients measured by Doppler techniques correlated well with the severity of coarctation.[1-3] In some patients after coarctation repair, however, we found increased velocities in the descending aorta not associated with clinically significant coarctation. These high velocities may be related to turbulence around the operation site. The flow velocity pattern in the descending aorta in coarctation can be abnormal in diastole as well as in systole.[4 5] Studies of the duration of flow in the descending aorta with measurements of acceleration time and anterograde flow time improved the correlation between catheterisation pressure gradients and Doppler derived gradients.[6] However, measurements related to flow duration were not studied in detail. We therefore further investigated ways in which gradients and flow patterns in the descending aorta can be used to predict the angiographic severity of coarctation.

Patients and methods

Between January 1987 and June 1989 we studied 17 children with coarctation of the aorta who had cardiac catheterisation and continuous wave Doppler studies performed within 48 hours of each other. Doppler studies were performed with either a Doptek Spectrascan or a Hewlett Packard (Model 77020AC) 2·5 MHz probe. An electrocardiogram was recorded simultaneously on paper at 100 mm/s speed. Seven patients underwent angioplastic balloon dilatation and measurements were taken before and after the procedure. Thus 24 pairs of measurements were available for analysis. We used continuous wave Doppler echocardiography from a standard suprasternal position to measure maximum velocity in the descending aorta. We measured the following variables (fig 1) and calculated gradients using the modified Bernoulli equation (gradient = $4V^2$)[7]: (*a*) instantaneous peak systolic gradient (mm Hg) corresponding to the maximal measured velocity; (*b*) early (peak) diastolic gradient (mm Hg) arbitrarily measured at the end of the T wave on the electrocardiogram; (*c*) systolic velocity half time (ms)—that is, time to half peak systolic velocity from the onset of

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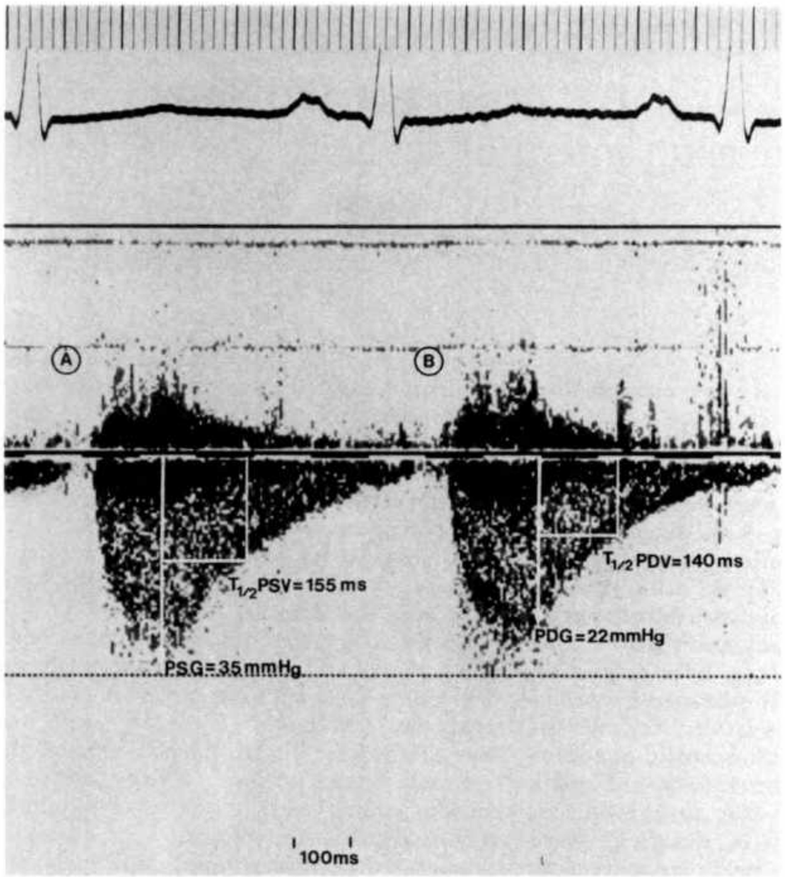

Figure 1 Continuous wave Doppler echocardiogram recorded from a suprasternal position in a patient with severe coarctation, showing systolic (A) and diastolic (B) measurements. PSG or PDG, peak systolic or diastolic gradient; $T\frac{1}{2}$ PSV or $T\frac{1}{2}$ PDV, time to half peak systolic or diastolic velocity.

ejection; and (*d*) diastolic velocity half time (ms)—that is, time taken for the diastolic velocity to fall to half its (peak) early value (at the end of the T wave).

We studied systolic frames that showed the maximal diameter on the aortogram or left ventriculogram and which showed the coarctation site and descending aorta at the level of the diaphragm. A diagram was copied from the projected aortogram in straight lateral or left anterior oblique view in all but two patients, when an anteroposterior projection was used. To control for age, weight, and *x* ray magnification, we measured the minimal diameter of the coarctation and expressed it as a ratio of the descending aorta at the level of the diaphragm (fig 2). Two independent observers analysed 22 of the 24 angiograms without previous knowledge of the measurements and subjectively graded the coarctation as severe, moderate, mild, or non-existent.

ANALYSIS OF DATA

The observer's subjective (but blind) angiographic assessment of severity was compared with the angiographic ratio. The data were evaluated for interobserver variablity, for the relation of subjective category to angiographic ratio, and for whether Doppler measurements and angiographic ratio correlate with decision to intervene. The angiographic ratio was used as the reference standard for the non-invasive measurements obtained with continuous wave Doppler.

Each of the Doppler measurements and the angiographically determined ratios were placed in rank order. Matrices of Spearman rank correlation coefficients for the basic data were then calculated to identify which Doppler measurements, when analysed as independent measurements, correlated with the angiographic index of severity.

Results

Table 1 shows the results of all measurements.

ANGIOGRAPHIC ASSESSMENT (TABLE 2)

All patients with an angiographic ratio $\leqslant 0{\cdot}5$ were considered to have severe or moderately severe coarctation by both observers and to require relief of the coarctation (surgery or balloon dilatation). All angiograms with ratios $>0{\cdot}65$ were graded as mild or trivial coarctation by both observers and were not regarded as requiring intervention. In five patients the ratios were between 0·5 and 0·65, and two (ratios 0·58 and 0·63) of these patients were considered to have none/mild coarctation by both observers. In the remaining three patients (ratios 0·57, 0·6, and 0·63) the coarctation was regarded as mild by one and moderate by the other observer. None of these three cases was regarded by the observers as requiring (nor did they undergo) intervention.

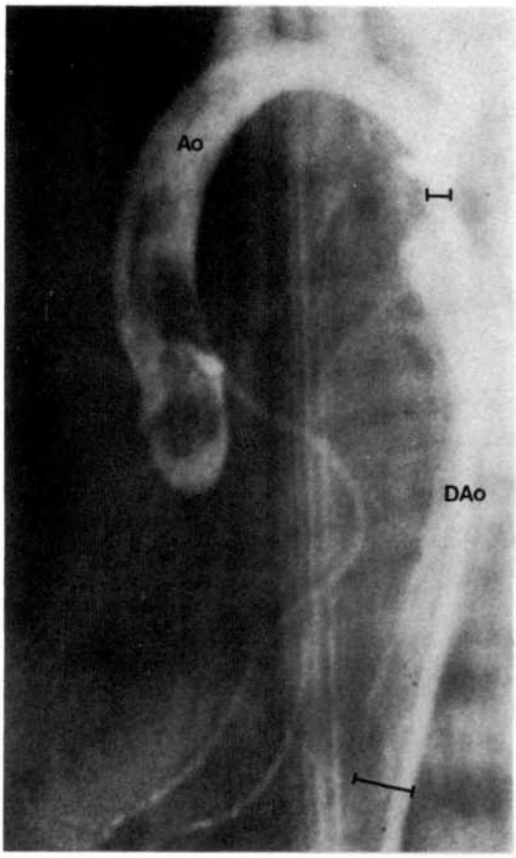

Figure 2 Systolic frame in lateral projection of an angiogram of the ascending aorta. The measurements of coarctation diameter and diameter of descending aorta at the level of diaphragm that were used to calculate the angiographic ratio are shown.

Table 1 Measurements by Doppler echocardiography and angiography

Patient		Ratio	PSG (mm Hg)	PDG (mm Hg)	T½PSV (ms)	T½PDV (ms)
1	Before	0·33	49	32	210	135
1	After	0·72	29	9	120	30
2		0·68	28	6	90	45
3	Before	0·50	50	35	105	55
3	After	0·63	17	1	60	50
4	Before	0·63	33	28	120	80
5	Before	0·57	18	5	100	20
6		0·49	21	16	160	135
7		0·45	52	44	260	215
8		0·13	63	50	325	335
9		0·29	25	23	150	125
10		0·22	45	32	370	400
11	Before	0·43	39	2	110	10
12	Before	0·30	43	27	85	35
12	After	1·00	17	0·7	110	0
13	Before	0·41	60	48	135	125
13	After	0·82	14	4	110	25
14		0·27	12	5	175	240
15	Before	0·25	37	20	200	120
15	After	0·60	33	6	120	20
16	Before	0·20	55	30	245	170
16	After	0·57	32	11	155	80
17	Before	0·27	31	12	120	130
17	After	0·80	12	0	85	0

Before and After refer to balloon dilatation.
PSG or PDG, peak systolic or diastolic gradients; T½, time to half peak systolic or diastolic velocity.

Table 2 Angiographic assessment of severity of coarctation

Patient		Ratio	Observer 1	Observer 2
1	Before	0·33	Severe	Severe
1	After	0·72	Mild	Mild
2		0·68	Mild	Mild
3	Before	0·50	Severe	Severe
3	After	0·63	Moderate	Mild
4	Before	0·63	Mild	Mild
5	After	0·57	Moderate	Mild
6		0·49	Severe	Severe
7		0·45	Moderate	Moderate
8		0·13	Severe	Severe
9		0·29	Severe	Severe
10		0·22	Severe	Severe
11	Before	0·43	Severe	Mod severe
12	Before	0·30	NA	NA
12	After	1·00	NA	NA
13	Before	0·41	Severe	Severe
13	After	0·82	None	None
14		0·27	Severe	Mod severe
15	Before	0·25	Severe	Mod severe
15	After	0·60	Moderate	Trivial
16	Before	0·20	Severe	Severe
16	After	0·58	None	Trivial/none
17	Before	0·27	Severe	Severe
18	After	0·80	None	None

NA, not available; Mod severe, moderately severe. Before and After refer to balloon dilatation.

DOPPLER ASSESSMENT

Because none of the patients with an angiographic ratio >0·5 was thought by either observer to require surgery or balloon dilatation, we elected to make this value a clinically important discriminant. We therefore examined the sensitivity and specificity of Doppler measurements for detecting patients with ratios above and below this value.

High systolic gradients or long decay times were specific for significant coarctation. In this series we obtained 100% specificity and 100% predictive value for detecting coarctation with an angiographic ratio ≤0·5 if the peak systolic gradient was >40 mm Hg and/or time to half peak diastolic velocity was >100 ms. Conversely, lower sensitivities were seen for each of the individual measurements, although diastolic variables were more sensitive and had better predictive values for a negative test than systolic measurements. This relatively low sensitivity of the Doppler technique was greatly improved when we considered the peak systolic gradient and peak diastolic velocity half time together—that is, whether there was either a peak systolic gradient >40 mm Hg or a long time to half peak diastolic velocity (>100 ms) (table 3). A plot of the angiographic ratios and time to half peak diastolic velocity shows the validity of this particular measurement (fig 5).

Matrices of the Spearman correlation coefficient showed that each of the individual Doppler measurements correlated with the angiographic ratio. Table 3 gives details of each correlation coefficient and significance level. All values were significant ($p < 0·003$), but the negative correlations between times to half peak systolic and to half peak diastolic velocities and the angiographic ratios were stronger than the correlation between peak systolic and diastolic gradients and the angiographic ratios. So it is likely that the longer the time to half maximal velocities (persistence of flow in diastole) the smaller the ratios (the more severe the coarctation).

Discussion

In the presence of coarctation of the aorta various factors can influence the flow pattern in the descending aorta.[8] The cross sectional area and length of the narrowed segment and the presence of a collateral circulation or a large ductus arteriosus are contributing factors, as is the cardiac output. The resultant pattern of flow to the descending aorta is, therefore, related to a complex interaction of all these factors. The limitations of using the Doppler technique to diagnose coarctation of the aorta in neonates have been recently emphasised.[9]

The pattern of flow velocity in the descending aorta in the presence of coarctation is qualitatively characteristic. High systolic velocities reflect the presence of a pressure drop between the proximal and distal aorta during ejection. High velocities also persist during diastole. In mild cases these have returned to baseline by mid diastole; but when coarctation is more severe, high velocities continue throughout diastole. It thus seems to us that not only might the patterns of diastolic flow provide a means of measuring the severity of coarctation but also that such patterns may reflect an aspect of the disturbance to normal physiology quite distinct from a simple reduction in peak perfusion pressure. This diastolic pressure drop can be considered as equivalent to a potential generated by a capacitance decaying across a resistance; so it can be modelled as an exponential. We therefore chose to measure its severity as a simple velocity half time. Obviously, conditions are more complex than this, particularly where there is a large collateral flow which could cause pressure to equilibrate rapidly regardless of the severity of the coarctation itself. Even so, we believed that measuring the decay time would give information related to the severity of obstruction in the presence of collaterals, and that the clinical value of such measurement might usefully be explored.

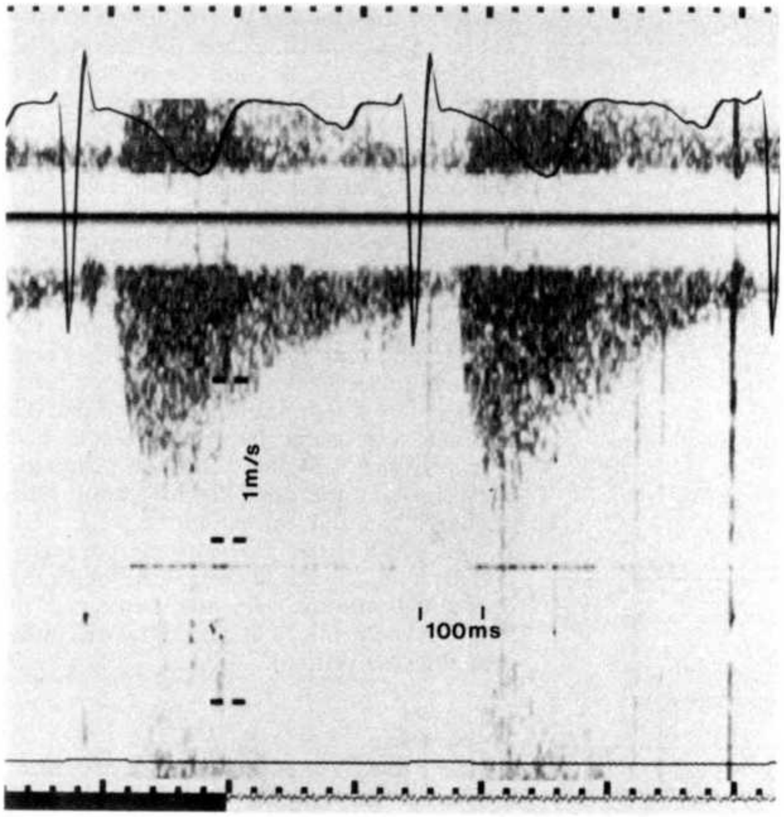

Figure 3 Continuous wave Doppler echocardiogram recorded in a patient with severe coarctation of the aorta (ratio = 0·27). Note slight increase in maximal systolic velocity (gradient = 12 mm Hg) but long diastolic velocity half time (240 ms).

Our results showed that the specificity of Doppler measurements in identifying severe coarctation of the aorta is high if there is an important gradient or flow that is maintained in diastole. In six patients severe coarctation would have been missed if only high peak systolic gradients had been considered. This low sensitivity could be greatly improved by analysing the peak diastolic velocity half time. This approach makes it possible to identify those patients with severe coarctation in whom lower velocities (and consequently lower gradients) are present. In this series only one patient (case 11) with a severe lesion would not have been definitely identified by the combination of the two measurements. However, even in this case the peak systolic gradient was nearly 40 mm Hg.

This analysis shows that the validity of the Doppler technique for assessment of severity of coarctation of the aorta can be significantly improved by the additional assessment of flow patterns. The factors that influence the presence of high velocity across the narrowed segment or persistence of flow in diastole in the descending aorta are certainly complex, but the presence of only one of these measurements seems to be enough to confirm that the coarctation is appreciable and warrants intervention. A very small number of patients, however, may still require cardiac catheterisation if measurements are borderline and there is uncertainty about the severity of coarctation on clinical grounds.

Table 3 Performance of Doppler echocardiographic measurements in detecting coarctation when the angiographic ratio was ≤ 0·5

	Sensitivity (%)	*Specificity (%)*	*Predictive value of positive test (%)*	*Predictive value of negative test (%)*	*Spearman rank correlation (p)*
PSG > 40 mm Hg	57	100	100	63	−0·57 (0·003)
T½ PSV > 140 ms	64	90	90	64	−0·67 (< 0·001)
PDG > 15 mm Hg	79	90	92	75	− 0·61 (0·001)
T½ PDV > 100 ms	79	100	100	77	− 0·76 (< 0·001)
PSG > 40 mm Hg or T½ PDV > 100 ms	93	100	100	91	

PSG or PDG, peak systolic or diastolic gradients. T½ PSV or T½ PDV, time to half peak systolic or diastolic velocity.

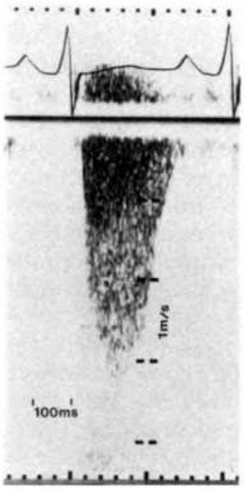

Figure 4 Continuous wave Doppler echocardiogram recorded in a patient with severe coarctation (ratio = 0·30), high peak systolic gradient (43 mm Hg), and short decay time (35 ms).

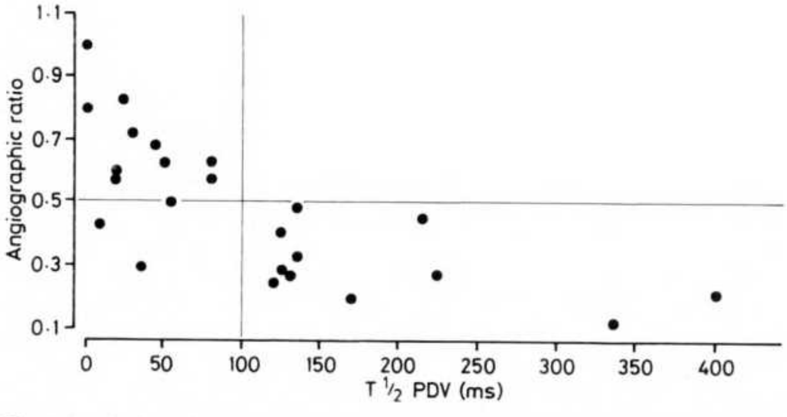

Figure 5 Angiographic ratio plotted against time to half peak diastolic velocity to show the validity of this measurement. There were no false positive (right upper corner) and three false negative results (left lower corner). True positive measurements are shown in the right lower corner and true negative on the left upper corner.

1 Wyse RKH, Robinson PJ, Deanfield JE, Tunstall Pedoe DS, Macartney FJ. Use of continuous wave Doppler ultrasound velocimetry to assess the severity of coarctation of the aorta by measurement of aortic flow velocities. *Br Heart J* 1984,52:278–83.

2 Robinson PJ, Wyse RKH, Deanfield JE, Franklin R, Macartney FJ. Continuous wave Doppler velocimetry as an adjunct to cross sectional echocardiography in the diagnosis of critical left heart obstruction in neonates. *Br Heart J* 1984;52:552–6.

3 Marx GR, Allen HD. Accuracy and pitfalls of Doppler evaluation of the pressure gradient in aortic coarctation. *J Am Coll Cardiol* 1986;7.1379–85.

4 Hatle L, Angelsen B. *Doppler ultrasound in cardiology: physical principles and clinical applications*. Philadelphia Lea and Febiger, 1985·217–21.

5 Houston AB, Simpson IA, Pollock JCS, Jamieson MPG, Doig WB, Coleman EN. Doppler ultrasound in the assessment of severity of coarctation of the aorta and interruption of the aortic arch *Br Heart J* 1987;57 38–43.

6 Syamasundar Rao P, Carey P. Doppler ultrasound in the prediction of pressure gradients across aortic coarctation. *Am Heart J* 1989;118 299–307.

7 Hatle L, Angelsen B. *Doppler ultrasound in cardiology· physical principles and clinical applications*. Philadelphia: Lea and Febiger, 1985:24.

8 Teirstein PS, Yock PG, Popp RL. The accuracy of Doppler ultrasound measurement of pressure gradient across irregular, dual and tunnellike obstructions to blood flow. *Circulation* 1985;72:577–84.

9 Wilson N, Sutherland GR, Gibbs JL, Dickinson DF, Keeton BR. Limitations of Doppler ultrasound in the diagnosis of neonatal coarctation of the aorta. *Int J Cardiol* 1989;23 87–9.

Br Heart J 1990;64:138–45

Morphological evaluation of atrioventricular septal defects by magnetic resonance imaging

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Abstract

Twelve patients aged between 2 weeks and 22 months (median 6 weeks) with atrioventricular septal defects were examined with a 1·5 T, whole body, magnetic resonance imaging system. Ten patients had a common atrioventricular orifice (complete defect) while two patients had separate right and left valve orifices (partial defect). Associated cardiac malformations included the tetralogy of Fallot in two, isomerism of the right atrial appendages and pulmonary atresia in two, and right isomerism and double outlet right ventricle in one. All had previously been examined by cross sectional echocardiography. Eight subsequently had angiography and six underwent surgical correction. There was one operative death and three other deaths. Three of these patients underwent postmortem examinations. Small children and infants were scanned inside a 32 cm diameter head coil. Multiple electrocardiographically gated sections 5 mm thick, separated by 0·5 mm, were acquired using a spin echo sequence with echo time of 30 ms. A combination of standard and oblique imaging planes was used. Magnetic resonance imaging was more accurate than echocardiography in predicting the size of the ventricular component of the defect. It was also better than either echocardiography and angiography in identifying the presence of ventricular hypoplasia. All these findings were confirmed by surgical or postmortem examinations or both.

Magnetic resonance imaging is capable of providing detailed morphological information in children with atrioventricular septal defects which is likely to be of value in their management.

Atrioventricular septal defects encompass a group of lesions associated with an underlying abnormality of the atrioventricular junction. These include a defect at the anticipated site of the muscular and atrioventricular septal structures of the normally septated heart. As there is no contiguity between atrial and ventricular septal structures, a common atrioventricular junction is present. There is basically a common atrioventricular valve with an abnormal arrangement of its valvar leaflets. Considerable variation occurs within this group of abnormalities. In particular, ventricular dominance of either the morphologically left or right ventricle may be present in association with hypoplasia of the opposite ventricle. Furthermore, there is a frequent association with other cardiac malformations.[1] In each case, these anatomical features will be fundamental in determining prognosis.[2] It follows that a comprehensive evaluation of the cardiac anatomy is crucial in managing patients with this malformation. Cross sectional echocardiography is the major non-invasive method used to demonstrate this anatomy and often it is the only technique used before surgery.[3] Invasive studies, however, are required when echocardiography fails to define the anatomy adequately.

Magnetic resonance imaging is a non-invasive technique capable of producing high resolution images of intracardiac anatomy in infants and children with congenital heart disease.[4–6] One of its major strengths is the ability to acquire images in any plane. Imaging protocols can be adapted to suit the anatomy of individual patients. This makes it particularly valuable for studying malformations such as atrioventricular septal defects, where there may be considerable morphological variation. With these considerations in mind, we studied the ability of magnetic resonance imaging to provide an accurate morphological assessment of the cardiac abnormalities associated with atrioventricular septal defects, noting particularly those features of surgical importance.

Patients and methods

PATIENTS

Between March 1988 and March 1989 all new patients seen at Guy's Hospital with a diagnosis of atrioventricular septal defect, confirmed by cross sectional echocardiography, were invited to enter the study. Informed consent was first obtained from parents or guardians of the children and infants. Only the parents of one child declined and twelve patients were examined. The median age of the group was 6 weeks (range 2 weeks to 22 months). Seven patients had Down syndrome. Associated malformations included the tetralogy of Fallot in two patients, isomerism of the right atrial appendages with pulmonary atresia in two patients, and right isomerism with double outlet right ventricle and hypoplastic pulmonary arteries in one patient. After magnetic resonance imaging, eight patients underwent angiography. Six of these have since undergone

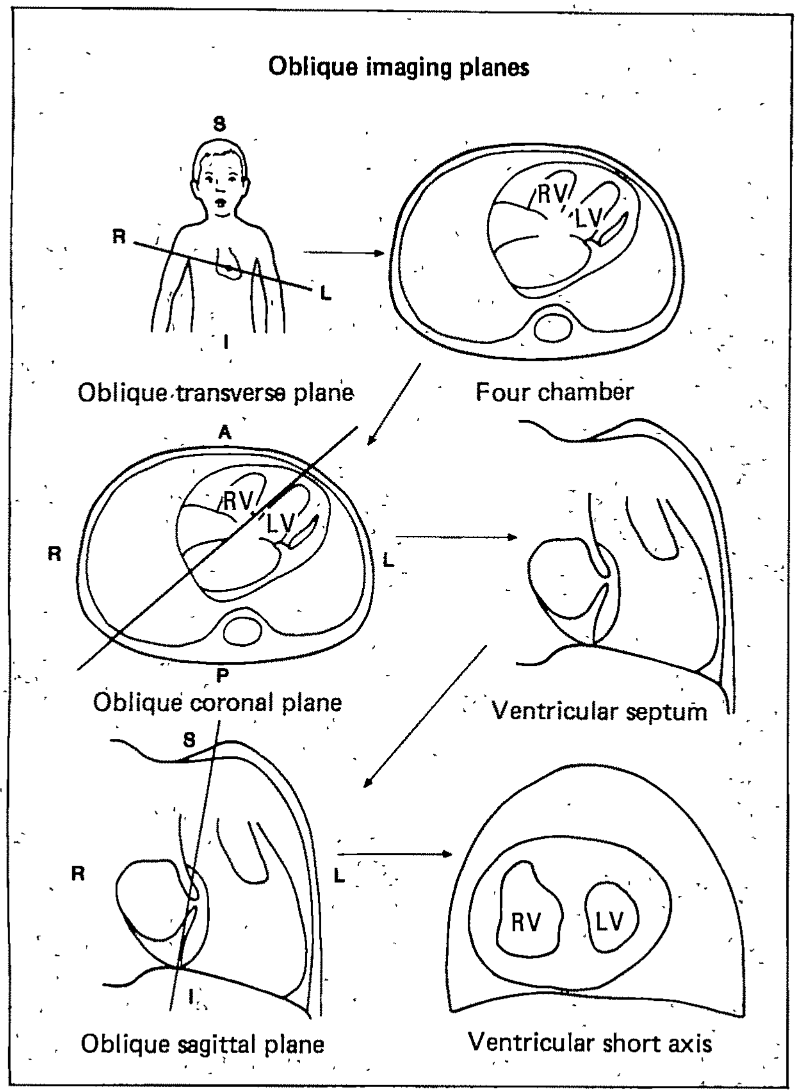


Figure 1 Frequently used imaging planes. Sections from an oblique transverse imaging plane produce a four chamber view. Sections directed along the plane of the ventricular septum (oblique coronal) give a face on view of the outline of the ventricular septum. From this view, a plane through the atrioventricular valve (oblique sagittal) produces a short axis view.

corrective surgery and three patients have been treated palliatively with modified Blalock-Taussig shunts. Three patients who were not suitable for early corrective surgery died. One patient undergoing corrective surgery also died in the early postoperative period. Three of these patients underwent a postmortem examination.

METHODS

Images were obtained with a 1·5 T, whole body, imaging system (Philips Gyroscan). Infants and smaller children were positioned inside a standard 32 cm proton head coil. All were sedated with chloral hydrate (50–75 mg/kg). Simultaneous sections, 5 mm thick, separated by 0·5 mm and gated to the patients' electrocardiogram, were acquired using a T1 weighted spin echo sequence with an echo time of 30 ms. Although the size of the matrix was 256 × 256, only 180 signals were used to construct the final image; so that the scanning times could be shortened with only a slight reduction in resolution of the images. The field of view was 200–250 mm. With two signal averages being performed for each examination, the typical scanning time for a series of seven sections was approximately 6 minutes.

Sections were acquired in orthogonal and oblique imaging planes, selected in each case by a cardiologist who was already familiar with the echocardiographic findings in the individual patient. Frequently used planes (fig 1) included an oblique transverse section, rotated around an anterior-posterior axis, to give a four chamber view; an oblique coronal plane, rotated around an inferior-superior axis, directed along the plane of the ventricular septum to provide a unique view of the inlet and trabecular portions of the ventricular septum face on; and an oblique sagittal plane, rotated around an inferior-superior axis as well as an anterior-posterior axis, to provide a short axis view of the ventricles and atrioventricular valve. The angles selected to obtain the oblique imaging planes were determined from the structures displayed in pre-existing images and they were varied to suit the anatomy of individual patients. The total scanning time for the complete examination was less than 90 minutes in every patient.

ANATOMICAL SPECIMENS

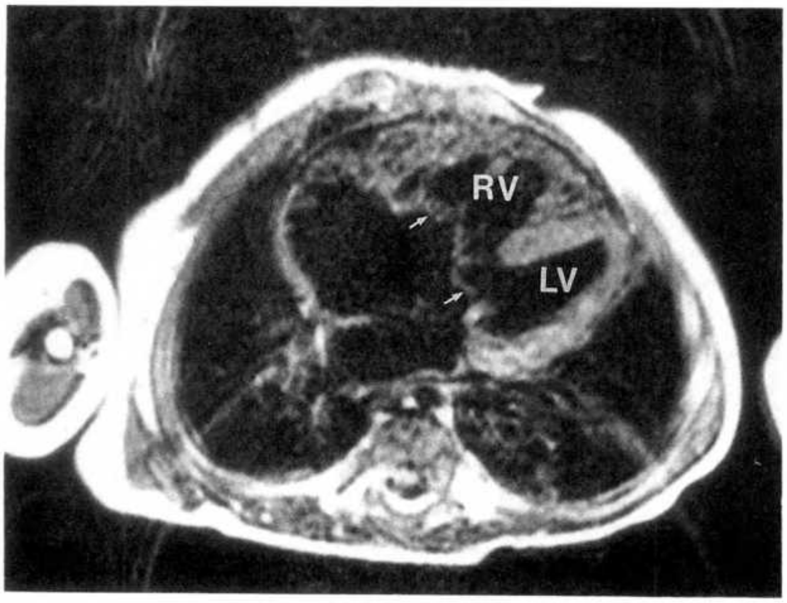
We dissected hearts from those patients who died in our series and specimens selected from the cardiopathological museum of the National Heart and Lung Institute to display the anatomy as it would be seen in cross section from imaging planes used by magnetic resonance imaging.

Results

There were no technical problems with this imaging protocol. Oral sedation proved effective in all cases and respiratory depression was not encountered. All the images were of diagnostic quality. The diagnosis of atrioventricular septal defect was most readily made from sections taken in a transverse plane. In patients with a common atrioventricular orifice both the atrial and ventricular components of the defect were identified. The presence of the common valve was detected by seeing that bridging leaflets were all at one level. The demonstration of both ventricles within a single image enabled their relative dimensions to be assessed (figs 2–4). In two patients who had separate right and left atrioventricular valve orifices we saw no ventricular component from this view (fig 3).

ATRIAL SEPTUM

No atrial septum was identified in the three patients with isomerism of the right atrial appendages. In the remaining nine patients, the atrial septum was shown in images taken in various planes. The oblique transverse plane was of greatest use in identifying the presence and size of the atrial component of the defect (figs 2, 5, and 6). We did not find bridging leaflets attached to the atrial septum, confining the anatomical potential for shunting at the ventricular level, in any of our patients. The four chamber view showed the characteristic "drum stick" appearance of the atrial septum



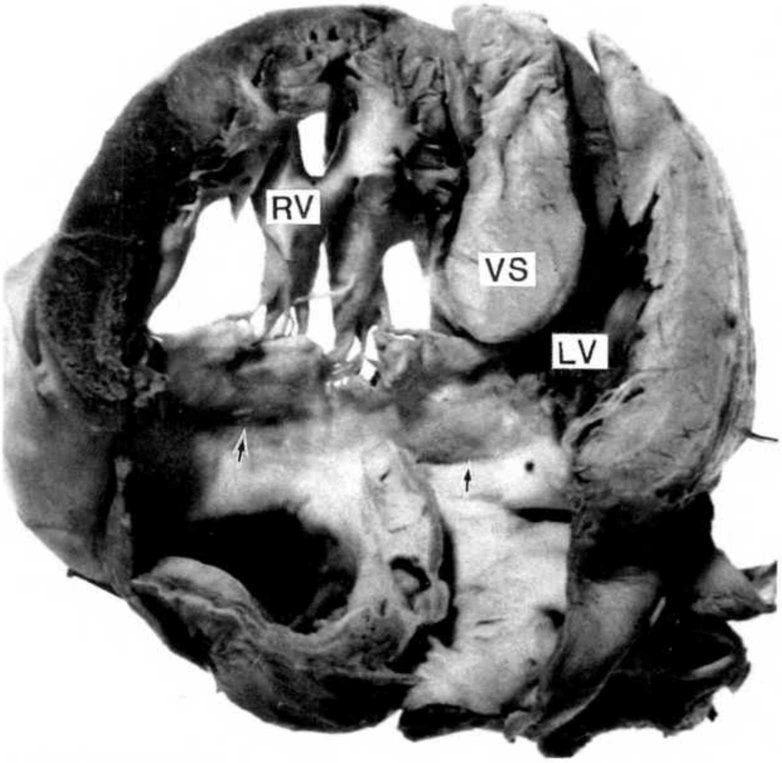


Figure 2 (Above) A section taken in an oblique transverse imaging plane from a patient (case 3) with atrioventricular septal defect and common valvar orifice. Both components of the defect are shown and the atrioventricular valves are at a common level (arrows). Relative ventricular dimensions can also be assessed from this view. RV, right ventricle; LV, left ventricle. (Below) A postmortem specimen from a different patient with atrioventricular septal defect and common valvar orifice, cut to show a four chamber view for comparison with the magnetic resonance imaging section. RV, right ventricle; LV, left ventricle; VS, ventricular septum; arrows = atrioventricular valve.

that is associated with an atrial component of the defect (fig 5).

VENTRICULAR SEPTUM

Because the ventricular septum is a three dimensional structure it was not possible to encompass it all within one single image. The use of serial sections in several planes enabled all its portions to be visualised. Images from transverse planes showed the muscular inlet, trabecular portions, and outlet portions (figs 2 and 3). An oblique coronal plane showed the scooped out muscular inlet portion, the muscular trabecular portion, and the outlet septum (figs 7–9). By using a combination of these views we could see the size of the ventricular component of the defect, if present, in every case, and correspondingly document its absence.

Because the heart lies obliquely within the thorax, the use of standard transverse planes often produced foreshortened views of the ventricle, the ventricular septum, and the ventricular component of the defect. In such cases, it was important to view sections in an oblique transverse plane (fig 1). Although images from this plane showed the ventricular component of the defect, it was often impossible to assess its size because attachments of the bridging leaflets to the ventricular septum obscured the defect (figs 6 and 10). Images taken from the oblique coronal plane directed along the ventricular septum, however, gave a unique view of its inlet and trabecular portions, which were seen face on. The ventricular component was identified from this view, appearing as a scooped out defect within the overall septum (figs 7 and 8) whose size was readily appreciated. Any sections that were inadvertently directed obliquely through the defect cut obliquely through the ventricular septum and failed to show the defect adequately. A repeat scan at a slightly different angulation ensured true alignment through the defect.

This view also showed the presence of attachments of the superior and inferior bridging leaflets to the crest of the ventricular septum (figs 7 and 8). In those patients with separate right and left atrioventricular valvar orifices the bridging leaflets of the valve and their connecting tongue were seen closely attached to the ventricular septum (fig 9), thus completely obliterating the ventricular component of the defect. Both the magnetic resonance image and the anatomical specimen in fig 9 show that there was no ventricular component to the defect. But you can still see that the scooped-out defect has the same dimensions as seen in patients with common valvar orifice (figs 7 and 8) although the anatomical potential for left-to-right shunting is entirely through the atrial component of the defect when the leaflets are firmly attached to the crest of the ventricular septum.

ATRIOVENTRICULAR VALVE

By using various imaging planes we saw and identified the superior and inferior bridging leaflets, together with their attachments to the ventricular septum. From a series of images taken in an oblique transverse plane, we found that the lowermost sections would include the inferior bridging leaflet while more cranial sections would include the superior bridging leaflet (fig 10). Images from an oblique coronal plane directed along the ventricular septum showed both the bridging leaflets together (figs 7 and 8).

We attempted to show the atrioventricular valve in the short axis view in oblique sagittal imaging planes. The results were universally disappointing. In only one patient was it pos-

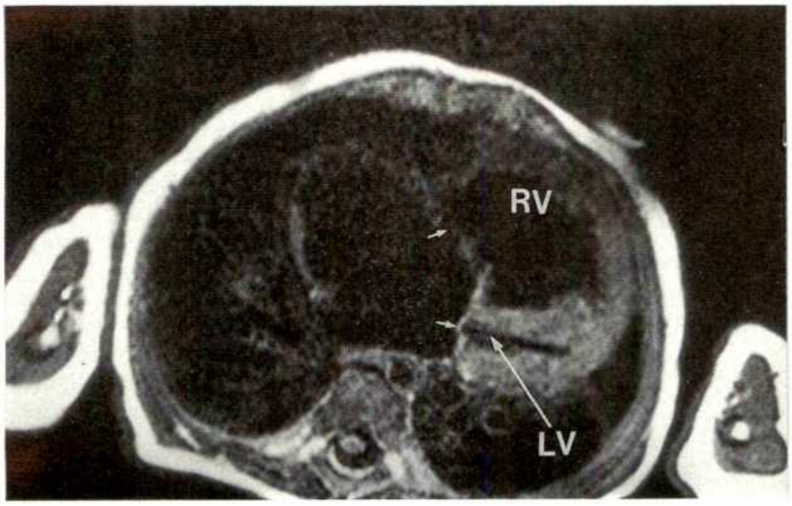


Figure 3 Four chamber view taken during early systole from patient 5 with an atrioventricular septal defect and separate right and left valve orifices. There was ventricular disproportion with hypoplasia of the morphologically left ventricle. The atrioventricular valves were inserted at the same level (arrows). No ventricular component of the defect was visible. RV, right ventricle, LV, left ventricle.

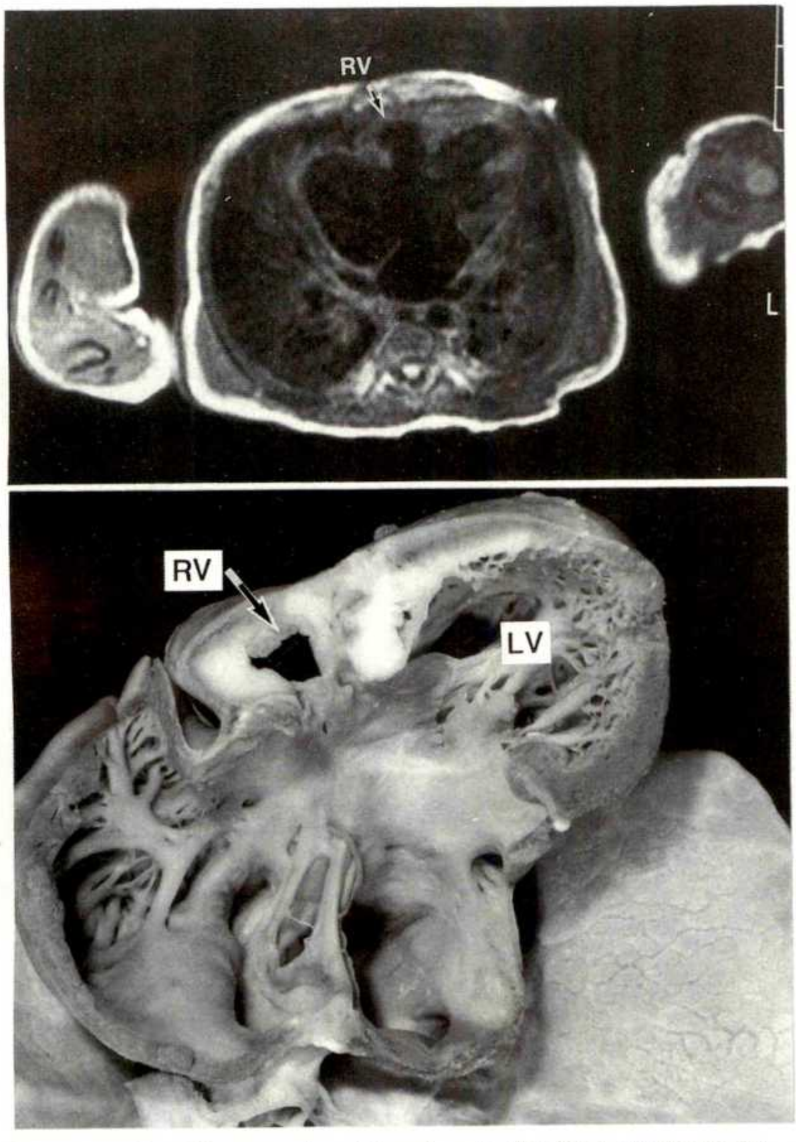


Figure 4 (Above) Transverse plane giving a four chamber view showing ventricular disproportion with a hypoplastic morphologically right ventricle (RV) in patient 12. Compare with figures 2 and 3. (Below) Anatomical specimen from the same patient showing hypoplastic morphologically right ventricle. RV, right ventricle; LV, left ventricle.

sible to see leaflets other than bridging leaflets. It was not possible in this plane to determine whether there was a common orifice or two separate atrioventricular valvar orifices. Papillary mucles within the left ventricle, however, were seen in this view. These were shown to have the superior-inferior relation known to be typical for this malformation (fig 11). Their distal insertions were not identified.

VENTRICULAR DIMENSIONS

The relative ventricular dimensions were assessed accurately in all patients. Oblique transverse imaging planes showed both ventricles side by side in long axis (figs 3, 4, and 6) and oblique sagittal imaging planes showed both ventricles together in an anterior-posterior relation in short axis (figs 11 and 12). Considerable ventricular hypoplasia of the morphologically left ventricle (figs 3 and 12) was shown in one patient and of the morphologically right ventricle in another (fig 4).

CORRELATION WITH ADDITIONAL INVESTIGATIONS

Six of the 12 patients have undergone corrective surgery. One patient died in the early postoperative period after corrective surgery. A late death occurred in a patient with hypoplastic pulmonary arteries who underwent palliative surgery. Two patients died without operation being performed. Necropsies were performed on three of the four patients who died. In all these cases, the accuracy of the findings at magnetic resonance imaging was confirmed. There were no major disagreements with the angiographic or echocardiographic findings (table). Magnetic resonance imaging was better than both echocardiography and angiography at showing the relative ventricular dimensions. In one patient hypoplasia of the morphologically left ventricle, correctly predicted with magnetic resonance imaging, was not fully appreciated with either of the other imaging techniques. Echocardiographic and angiographic assessment of the size of the ventricular component of the defect was made difficult in some patients because attachments of bridging leaflets to the ventricular septum often obscured the defect. Magnetic resonance imaging accurately showed the size of the defect in these cases through use of the oblique coronal plane which imaged the ventricular septum face on. Magnetic resonance imaging, however, was not good at identifying valvar leaflets other than the bridging ones and was not able consistently to show the distal insertion of the papillary muscles.

Discussion

Magnetic resonance imaging is particularly suited to the examination of congenital heart malformations.[4-6] It is non-invasive and does not require the use of ionising radiation. With appropriate imaging procedures, moving blood does not produce any signal. This means that high resolution images of vascular structures can be achieved without the use of contrast

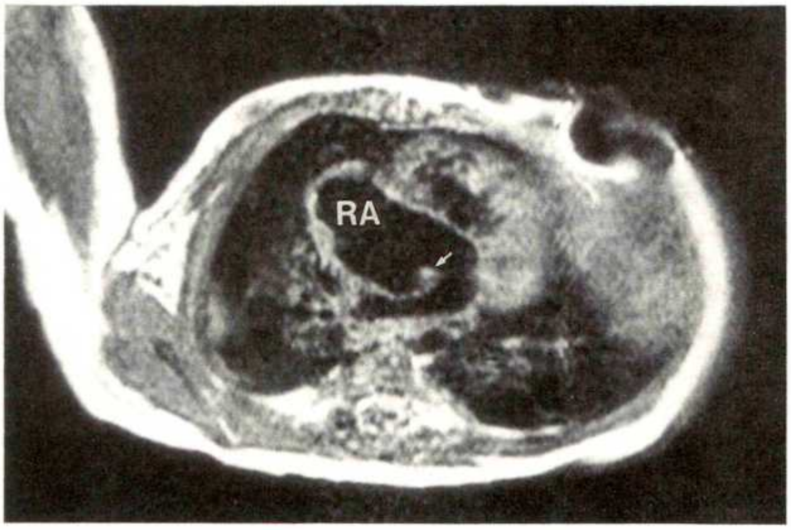


Figure 5 Section taken in a transverse imaging plane in patient 2 showing an atrial septum with the characteristic "drum stick" appearance associated with this defect (arrow). Note that the right atrium (RA) is larger than the left.

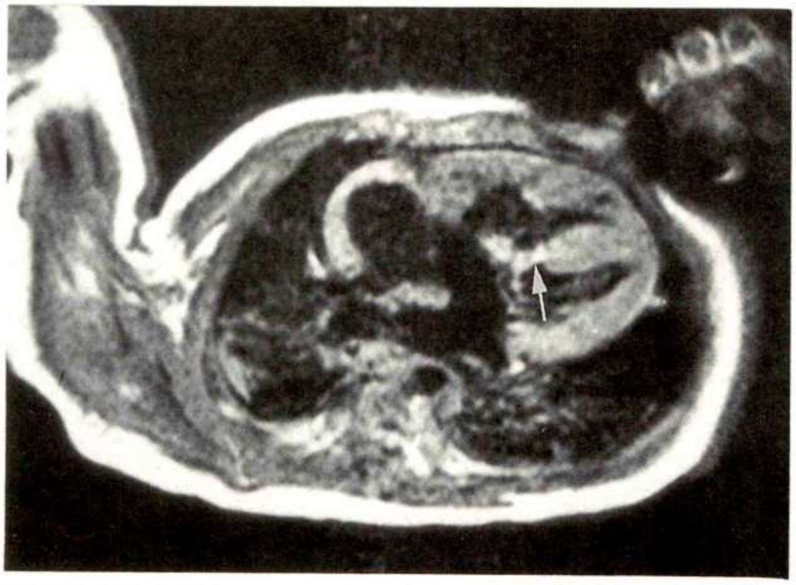


Figure 6 Patient 7 had a common atrioventricular orifice with a ventricular component. The size of the ventricular component, however, was not apparent from this four chamber view because it was obscured by dense attachments of the bridging leaflets to the crest of the ventricular septum (arrow).

agents. In addition, the image signal is not affected by the depth of structures within the thoracic cavity or by the presence of overlying bone or lung.

Our study differs in several important aspects from some of the earlier investigations of patients with atrioventricular septal defects.[7-9] First, because we used a magnet with a higher field strength we were able to study a group of much younger patients.[10] This is important because many patients need corrective operation in infancy. Such patients do not always require invasive haemodynamic evaluation. Preoperative investigation is often limited to cross sectional echocardiography.[3] Secondly, we made full use of oblique imaging planes. This was not done in earlier studies, which were limited to using only standard orthogonal planes.[7-9] Thirdly, we attempted to identify areas in which magnetic resonance imaging has advantages over existing imaging techniques and which can provide information of practical importance in construction of protocols for management.

Although it is straightforward to diagnose atrioventricular septal defect with magnetic resonance imaging (predominantly from a four chamber view, where the septal deficiency is readily seen), this feature alone is unlikely to be of any great practical use because in most patients the diagnosis will already have been achieved non-invasively with cross sectional echocardiography. The importance of magnetic resonance imaging, therefore, is likely to lie in the ability and accuracy in which it can identify anatomical features that are relevant to operation. It is often difficult to estimate with cross sectional echocardiography the size of the ventricular component of the defect, if present. In some cases, problems can arise in distinguishing between an atrioventricular septal defect with common valvar orifice and a small ventricular component from a defect with separate orifices and no potential for ventricular shunting[11]—that is when dense attachments between the bridging leaflets and the crest of the

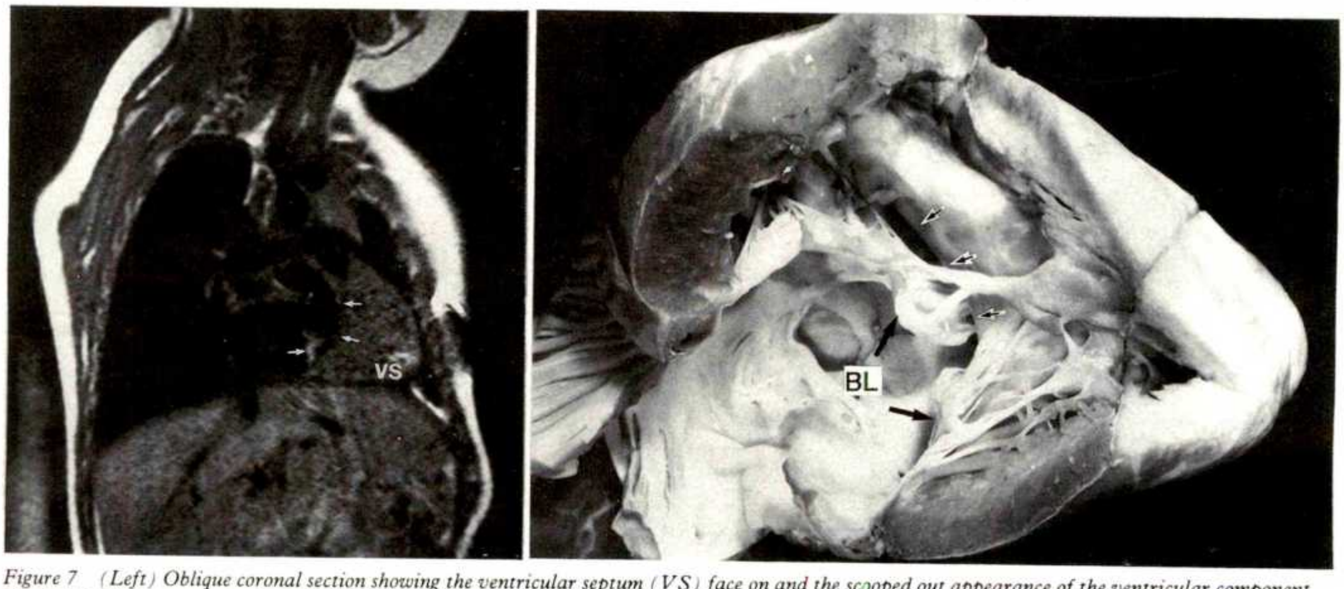


Figure 7 (Left) Oblique coronal section showing the ventricular septum (VS) face on and the scooped out appearance of the ventricular component of the defect (arrows) in patient 11. The inferior bridging leaflet was seen with attachments to the crest of the ventricular septum (single arrow). (Right) Anatomical specimen from the same patient. The ventricular component of the defect was seen (arrows) as well as bridging leaflets (BL) with attachments to the crest of the ventricular septum.

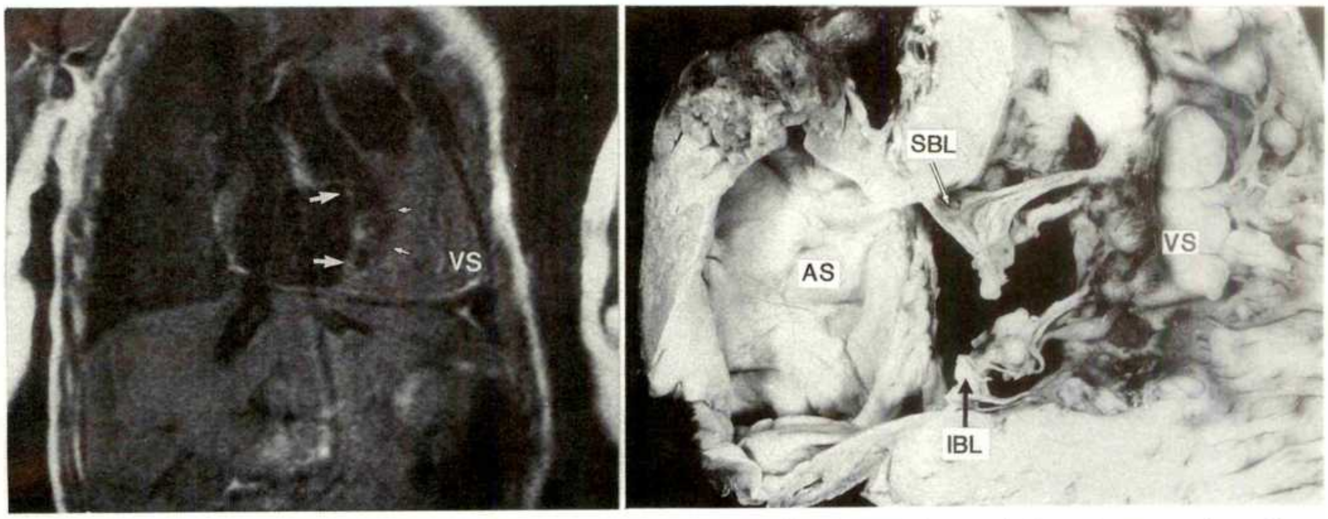


Figure 8 (Left) Section in an oblique coronal imaging plane from a patient (case 6) with atrioventricular septal defect and common valvar orifice. The ventricular septum (VS) was shown face on and free floating bridging leaflets (large arrows) were seen with attachments to the right ventricular aspect of the ventricular septum (small arrows). (Right) Postmortem specimen from a different patient cut in the same plane, demonstrating the anatomy shown in the magnetic resonance imaging section. SBL, superior bridging leaflet; IBL, inferior bridging leaflet; VS, ventricular septum; AS, atrial septum.

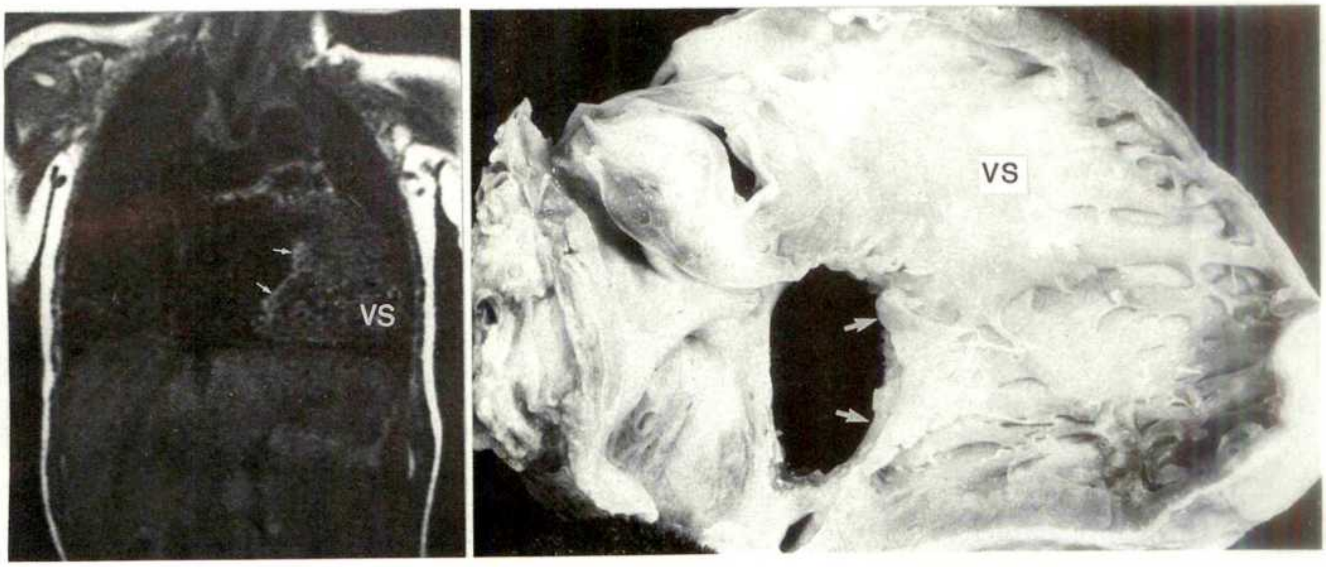


Figure 9 (Left) Oblique coronal section from patient 5. The bridging leaflets (arrows) can be seen closely attached to the ventricular septum (VS) obliterating the ventricular component of the defect. Compare with figures 7 and 8. (Right) Postmortem specimen from a different patient with separate right and left atrioventricular valve orifices, cut in a similar plane to compare with the magnetic resonance imaging findings. The bridging leaflets (arrows) are seen closely attached to the ventricular septum (VS).

ventricular septum obscure the ventricular component of the defect. Invasive investigations may then be necessary to make a decision on the timing of surgery.[3] Even with angiography, it can be difficult to differentiate between these defects.[12] The oblique coronal plane, which images the ventricular septum face on, is unique to magnetic resonance imaging. It is not possible with echocardiography or angiography (which is an imaging technique using projections rather than sections). As we showed, this view clearly outlined the component of the defect scooped from the ventricular septum. It also shows both bridging leaflets and identifies the degree of their attachments to the scooped out septum. In our two patients with separate valvar orifices and no ventricular component, it showed close approximation of the bridging leaflets to the crest of the ventricular septum with complete obliteration of the ventricular component. In all patients studied, magnetic resonance imaging was the most accurate imaging technique for assessing the presence and size of the ventricular component of the defect.

Another strength of magnetic resonance imaging is its ability to display cardiac structures in relation to the rest of the thoracic cavity. This allowed the chamber dimensions to be assessed immediately, enabling patients with atrial and, more importantly, ventricular disproportion to be identified. This observation is important because one determinant of surgical risk is the presence of ventricular hypoplasia.[2 13] Although this is relatively common it may be difficult to detect with echocardiography[14] and, indeed, angiography, as was the case in one patient of our series. Because

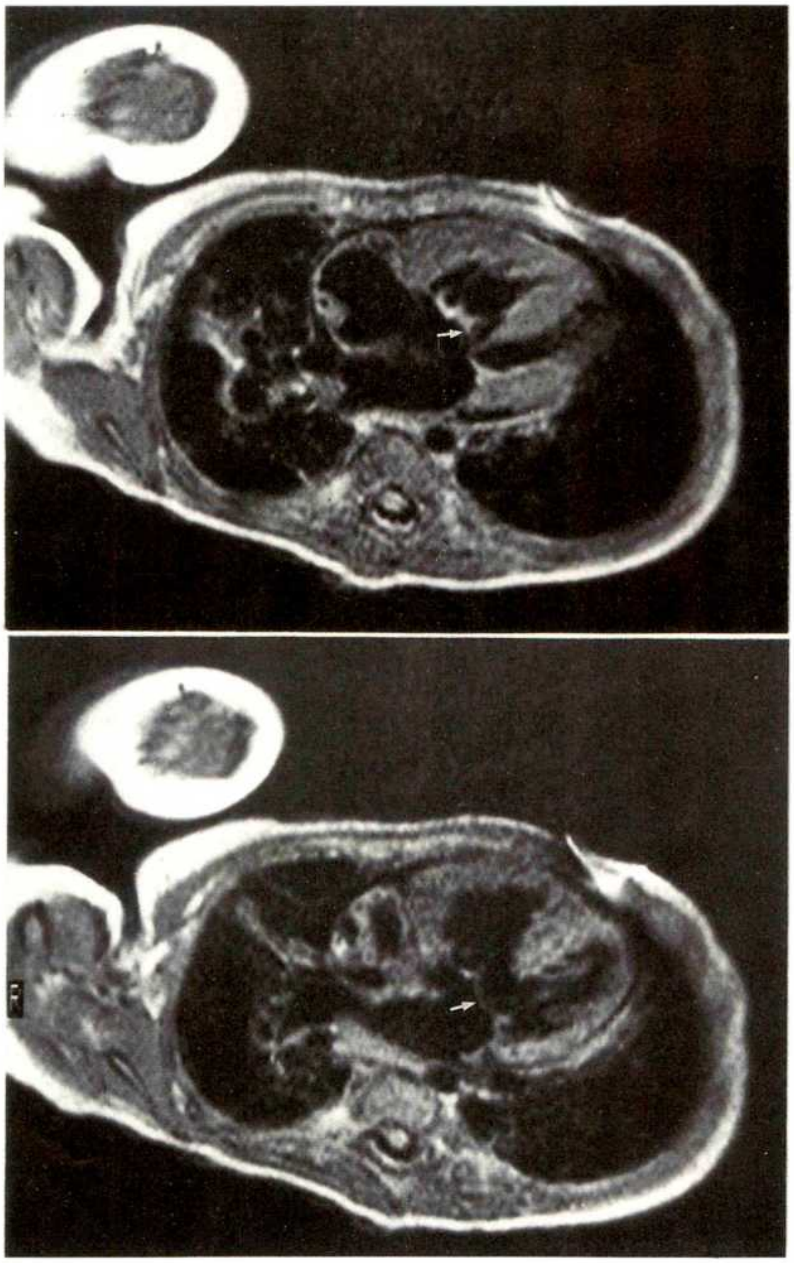


Figure 10 (Above) Transverse section from a patient with a common atrioventricular orifice showing inferior bridging leaflet (arrow) with attachments to the ventricular septum in patient 6. The ventricular component of the defect was not seen clearly. (Below) A more cranially directed section from the same patient. The superior bridging leaflet was free floating (arrow) and the ventricular component of the defect was visible.

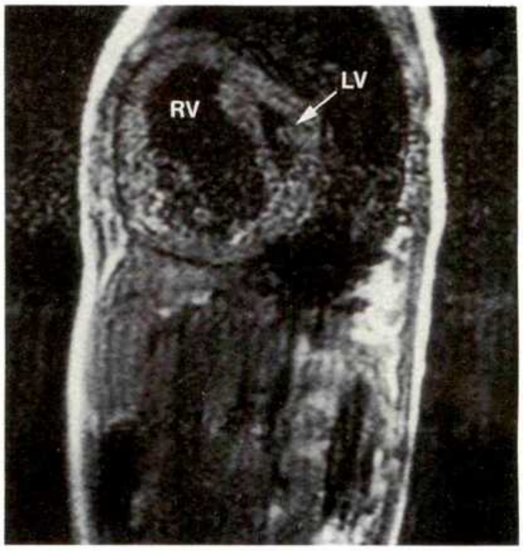


Figure 12 An oblique sagittal section showing both ventricles in short axis (patient 5). There was hypoplasia of the morphologically left ventricle. Compare with figure 10. RV, right ventricle; LV, left ventricle.

magnetic resonance imaging showed both ventricles in close relation to each other and in both short and long axis views, ventricular hypoplasia, when present, was more easily diagnosed.

In all of the patients who had corrective surgery or necropsy, the accuracy of the magnetic resonance images was confirmed and, apart from the areas previously discussed, there was good correlation with echocardiographic and angiographic findings. We have, however, identified some potential weaknesses of magnetic resonance imaging, including a failure to show clearly all leaflets of the atrioventricular valve and to show the insertions of their papillary muscles. Our current experience, therefore, suggests that magnetic resonance imaging can be of value in the management of patients with atrioventricular septal defects when cross sectional echocardiography is the only imaging technique used for evaluation before operation and where the cross sectional echocardiographic findings or the angiographic findings are in dispute. In such cases magnetic

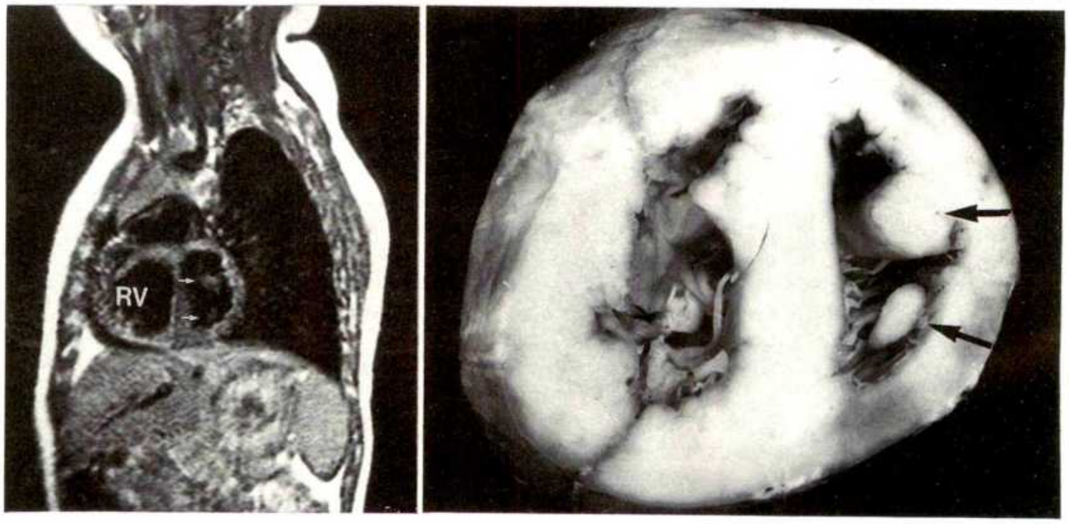


Figure 11 (Left) Oblique sagittal plane showing both ventricles in short axis in patient 11. The characteristic superior-inferior relation of papillary muscles (arrows) associated with atrioventricular septal defect was visible within the morphologically left ventricle. RV, right ventricle. (Right) Anatomical specimen from this patient cut in a similar plane. The superior-inferior relation of the papillary muscles (arrows) was visible within the morphologically left ventricle.

Patient details

Case No	*Age*	*Valvar morphology*	*Echo*	*Angio*	*Surgery*	*Necropsy*	*MRI findings*
1	2 wk	Common	+			+	Agreed
2	2 wk	Common	+	+	+		Agreed
3	14 mnth	Common	+	+	+		Agreed
4	9 days	Common	+	+			Agreed
5	10 mnth	Separate	+	+	+		Hypoplastic left ventricle
6	4 mnth	Common	+	+	+		Agreed
7	14 mnth	Common	+	+	+		Agreed
8	2 wk	Common	+				Agreed
9	18 mnth	Common	+	+			Agreed
10	22 mnth	Separate	+	+	+		Agreed
11	6 wk	Common	+			+	Agreed
12	1 wk	Common	+			+	Hypoplastic right ventricle

MRI, magnetic resonance imaging.

resonance imaging can complement morphological information obtained earlier and so improve diagnostic accuracy.

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1 Anderson RH, Macartney FJ, Shinebourne EA, Tynan M. *Paediatric cardiology*. Edinburgh: Churchill Livingstone, 1987:574–6.

2 Studer M, Blackstone EH, Kirklin JW, *et al.* Determinants of early and late results of repair of atrioventricular septal (canal) defects. *J Thorac Cardiovasc Surg* 1982;84: 523–42.

3 Kirklin JW, Barret-Boyes BG. *Cardiac surgery*. New York: Wiley Medical, 1986:561.

4 Baker EJ, Ayton V, Smith MA, *et al.* Magnetic resonance imaging of coarctation of the aorta in infants: use of a high field strength. *Br Heart J* 1989;62:97–101.

5 Baker EJ, Ayton V, Smith MA, *et al.* Magnetic resonance imaging at a high field strength of ventricular septal defects in infants. *Br Heart J* 1989;62:305–10.

6 Higgins CB, Byrd BF, Farmer DW, Osaki L, Silverman NH, Cheitlin MD Magnetic resonance imaging in patients with congenital heart disease. *Circulation* 1984;70:851–60.

7 Fletcher BD, Jacobstein MD, Nelson AD, Riemenschneider TA, Alfidi RJ. Gated magnetic resonance imaging of congenital cardiac malformations. *Radiology* 1984;150: 137–40.

8 Jacobstein MD, Fletcher BD, Goldstein S, Riemender TA. Evaluation of atrioventricular septal defect by magnetic resonance imaging. *Am J Cardiol* 1985;55:1158–61

9 Didier D, Higgins CB, Fischer MR, Osaki L, Silverman NH, Cheitlin MD. Congenital heart disease: gated MR imaging in 72 patients. *Radiology* 1986;158 227–35.

10 Smith MA, Baker EJ, Ayton V, Parsons JM, Ladusans EJ, Maisey MN. Magnetic resonance imaging of the infant heart at 1 5 T. *Br J Radiol* 1989;62:367–70.

11 Smallhorn JF, Tommasini G, Anderson RH, Macartney FJ. Assessment of atrioventricular septal defect by two dimensional echocardiography. *Br Heart J* 1982;47: 109–21.

12 Macartney FJ, Rees PG, Daly K, *et al.* Angiocardiographic appearances of atrioventricular defects with particular reference to distinction of ostium primum atrial septal defect from common atrioventricular orifice. *Br Heart J* 1979;42:640–56.

13 Kirklin JW, Barret-Boyes BG. *Cardiac surgery*. New York: Wiley Medical, 1986:579–83.

14 Mehta S, Hirschfeld S, Riggs T, Liebman J. Echocardiographic estimation of ventricular hypoplasia in complete atrioventricular canal. *Circulation* 1979;59:888–93.

Br Heart J 1990;64:146–50

An association between left axis deviation and an aneurysmal defect in children with a perimembranous ventricular septal defect

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Abstract

Conspicuous left axis deviation was found in two thirds (27 patients) of 44 children with a perimembranous ventricular septal defect, echocardiographic signs of apposition of the septal tricuspid valve leaflet, and an aneurysm of the membranous septum. In 10 patients earlier electrocardiograms did not show left axis deviation; this feature appeared when the aneurysm of the membranous septum was first seen on the echocardiogram. None of the 44 controls with perimembranous ventricular septal defect but without an aneurysm had left axis deviation.

This study suggests that the appearances of conspicuous left axis deviation in a patient with ventricular septal defect indicate a spontaneous reduction in the defect by apposition of the septal tricuspid valve leaflet and by the formation of an aneurysm of the membranous septum.

Extreme left axis electrocardiographic deviation is uncommon in children and is generally associated with complex congenital heart disease. We noticed that children with an isolated perimembranous ventricular septal defect and echocardiographic signs of a reduction in the size of the defect by the apposition of the septal tricuspid valve leaflet and the formation of an aneurysm often also had left axis deviation.

Patients and methods

We studied 44 patients, chosen at random, in whom cross sectional echocardiography showed a perimembranous ventricular septal defect that was partially closed by apposition of the septal tricuspid valve leaflet and an aneurysm of the membranous septum. We also studied 44 patients in whom cross sectional echocardiography showed a small to moderate perimembranous ventricular septal defect without apposition of the septal tricuspid valve leaflet or an aneurysm. They too were also chosen at random from those in whom echocardiography showed the relevant signs. We excluded patients with Down's syndrome or any other syndromes and children with other associated congenital heart diseases.

All three of us analysed the standard electrocardiograms of the 88 patients by calculating the QRS axis in the frontal plane and other characteristics of the tracings. We used Student's t test and the χ^2 test for statistical analysis. A QRS axis $> -30°$ was regarded as left axis deviation.[1]

Results

The mean age of patients with an aneurysm of the membranous septum was 3 years (range 1 month to 15 years) and in those without it was 2 years (range 1 month to 15 years). The table summarises the electrocardiographic findings in both study groups. Twenty seven (61%) of the 44 patients with an aneurysm of the membranous septum had conspicuous left axis deviation (fig 1). In the remaining 17 patients the QRS axis was more positive than 0° (mean +60·5°). None of the patients without an aneurysm of the membranous septum had left axis deviation. This difference was highly significant by both statistical tests: $t = 15\cdot28$, $p < 0\cdot001$; $\chi^2 = 40\cdot25$, $p < 0\cdot001$. The mean age at which the left axis deviation appeared or was detected in the 27 children with an aneurysm of the membranous septum was 2 years—70% were <2 years old, and 50% were <7 months old. Most of the patients in both study groups did not show electrocardiographic evidence of ventricular enlargement; a few showed slight to moderate left ventricular or biventricular enlargement.

Fifteen (34%) of the 44 patients with an aneurysm of the membranous septum had an incomplete right bundle branch block compared with only three (7%) patients from the group without an aneurysm: $\chi^2 = 10\cdot6$, $p \approx 0\cdot001$. Thirteen of the 27 patients with left axis deviation also had an associated right bundle branch block (fig 2). So half those with a left axis deviation also had a right bundle branch block.

In 10 of the 27 patients with left axis deviation (fig 3A) earlier electrocardiograms had not shown this feature. The appearance of this extreme left axis deviation coincided with clinical evidence that the defect had become smaller and echocardiographic demonstration of apposition of the septal tricuspid valve leaflet and an aneurysm of the membranous septum (fig 3B). (In five of the 10 patients left axis deviation and right bundle branch block occurred simultaneously.) The remaining 17 patients had left axis deviation at presentation.

Only seven patients with an aneurysm of the membranous septum were studied by

Electrocardiographic findings in patients with ventricular septal defect

		With AMS (44) n (%)	*Without AMS (44) n (%)*
QRS axis:			
−30° to −90°		27 (61·4)	0 (0)*
More positive than 0°		17 (38·6)	44 (100)
Mean		+60·5	+71·3
Chamber enlargement:			
None		25 (56·8)	26 (59·0)
Slight	LVE	11 (25·0)	9 (20·5)
Moderate	LVE	2 (4·6)	3 (6·8)
Considerable	LVE	0 (0)	1 (2·3)
Biventricular		6 (13·6)	5 (11·4)
Incomplete RBBB		15 (34·0)	3 (6·8)†
Left axis deviation and incomplete RBBB		13 (48·0)	0 (0)

*$p < 0·001$. †$p \approx 0·001$.
AMS, aneurysm of the membranous septum; RBBB, right bundle branch block; LVE, left ventricular enlargement.

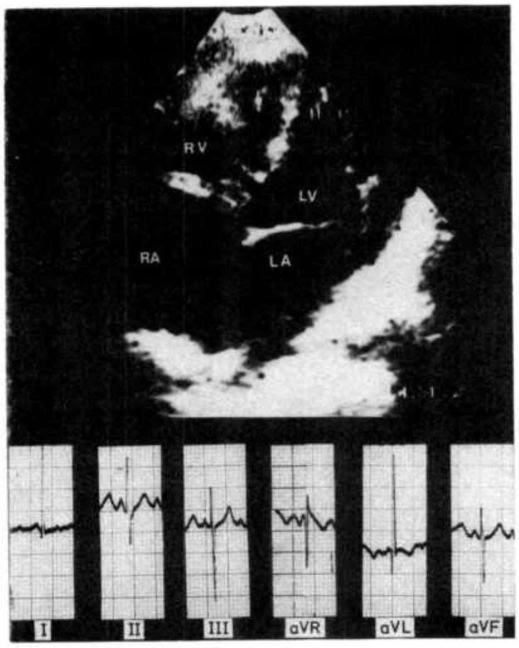

Figure 1 Cross sectional echocardiogram (apical four chamber view) and electrocardiogram showing perimembranous ventricular septal defect and aneurysm of the membranous septum. The electrocardiogram shows left axis deviation. RV, right ventricle; LV, left ventricle; RA, right atrium; LA, left atrium.

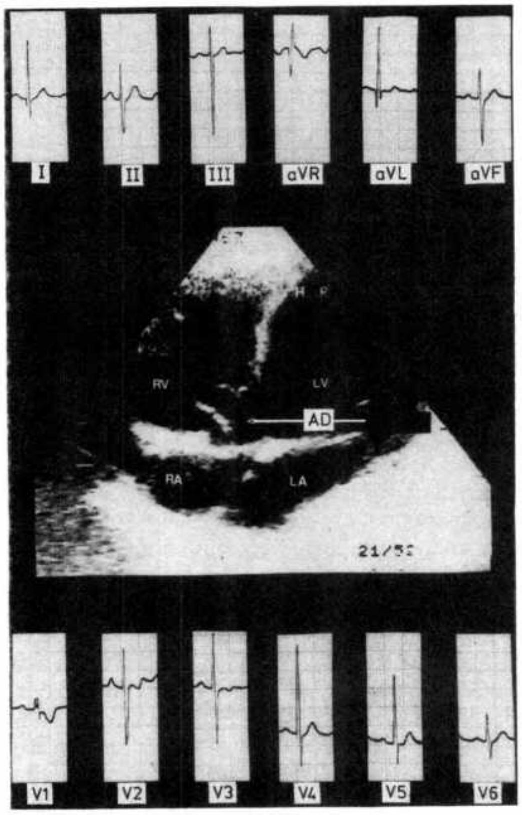

Figure 2 Cross sectional echocardiogram (apical four chamber view) and electrocardiogram showing ventricular septal defect and aneurysm of the membranous septum (arrow). The electrocardiogram shows left axis deviation and incomplete right bundle branch block. RV, right ventricle; LV, left ventricle; RA, right atrium; LA, left atrium; AD, aneurysmal defect.

cross sectional and Doppler echocardiography and all of them had slight to moderate tricuspid insufficiency (fig 4).

Discussion

Spontaneous closure of membranous ventricular septal defects was reported in between 25 and 80% of patients.[2-4] Apposition of the septal tricuspid valve leaflet and an aneurysm of the membranous septum have been suggested as important mechanisms reducing the size of the ventricular septal defect.[5 6] In 1957 Steinberg showed angiocardiographically that apposition of the septal tricuspid valve leaflet and an aneurysm of the membranous septum may be related to the spontaneous closure of the ventricular septal defect.[7] Since then many reports have indicated that the development of an aneurysm of the membranous septum is not only a common and benign finding in patients with ventricular septal defect but also that its appearance usually predicts a reduction in or even spontaneous closure of the ventricular septal defect.[6 8 9] Such features are common in patients with small ventricular septal defects. In the study on the course of aneurysms of the membranous septum by Freedom *et al*, 70% of the patients with small ventricular septal defect, who had a pulmonary-to-systemic blood flow ratio of <2, had an aneurysm of the membranous septum.[6] Nugent *et al* studied 119 patients with ventricular septal defects and found an aneurysm at angiography in 41% of them at 5·6 years of age and in 61% at 11 years of age.[10]

Beerman *et al* found that 45% of 87 patients with ventricular septal defect and an aneurysm of the membranous septum improved after a median follow up of 8·6 years (range 1·2–18·8). Only 5% had spontaneous closure of the defect.[9]

The only documented mode of closure of the more common defects of the membranous septum is the adherence of the medial leaflet of the tricuspid valve to the defect.[11-13]

Bäckman studied the QRS axis in 179 patients with ventricular septal defect. He found that the average QRS axis was +58·0°; 10·1% of them had an obvious or extreme axis deviation, $> -30°$.[1] Extreme left axis deviation was found in 1·4% of healthy infants and children.[14]

Bäckman pointed out that left axis deviation was more common when the ventricular septal defect lay beneath the septal leaflet of the tricuspid valve. Nevertheless, he concluded that it is not possible to establish the site of the defect by electrocardiographic recording.[1]

In our series the association between left electrical axis deviation and a ventricular septal defect beneath the septal leaflet of the tricuspid valve was clearly due not only to the anatomical site of the defect but also to the adherence of the septal tricuspid valve leaflet which reduced the size of the ventricular septal defect. This suggestion is supported by the fact that extreme left axis deviation was a new finding in 10 of the 27 patients.

It is evident that chamber enlargement can

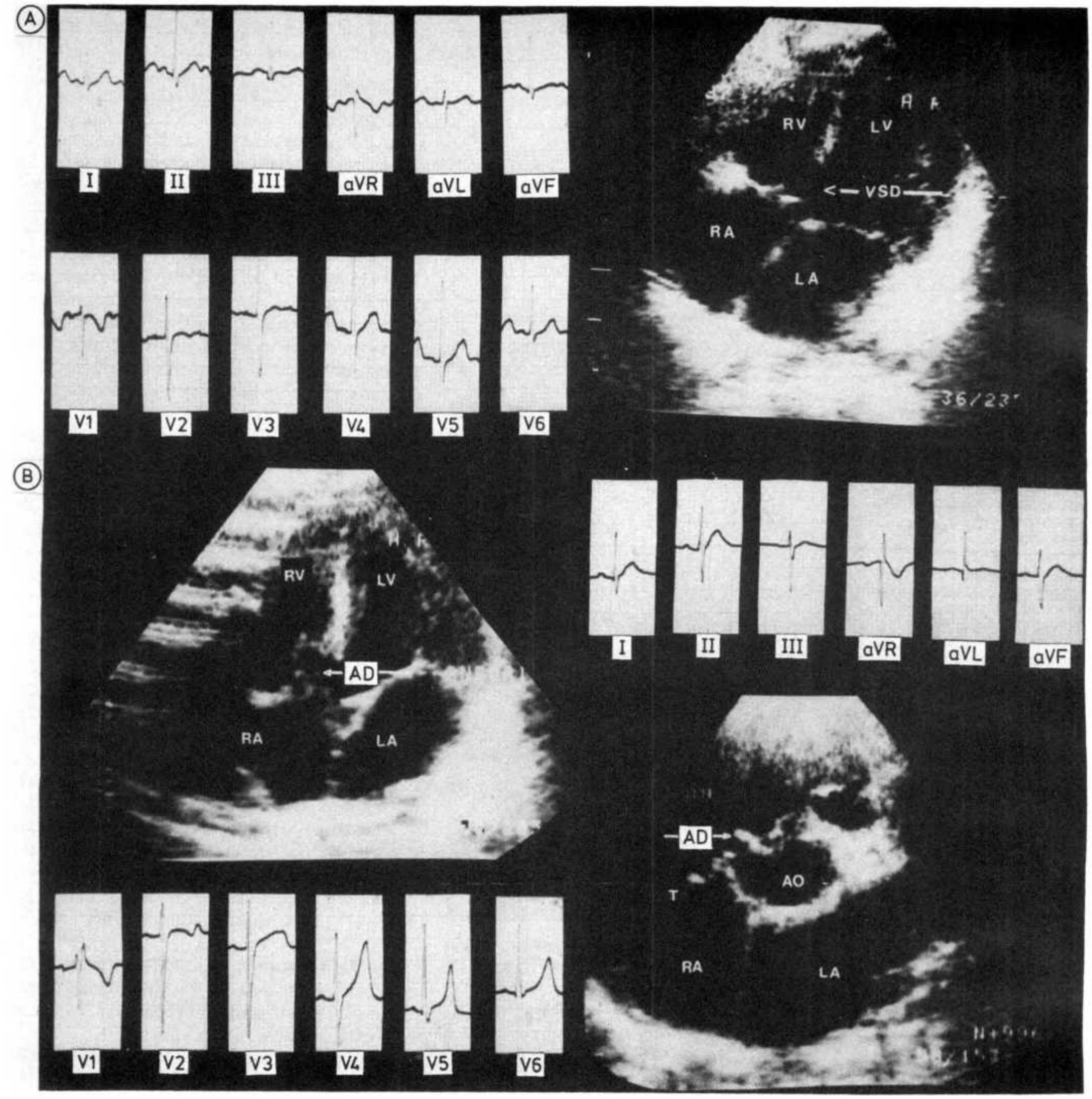

Figure 3 Cross sectional echocardiogram and electrocardiogram. (A) When the patient was three months old the echocardiogram (four chamber view) showed a small to moderate perimembranous ventricular septal defect (arrow) without an aneurysm of the membranous septum. There was no left axis deviation or right bundle branch block on the electrocardiogram. (B) When the patient was five years old the echocardiogram (four chamber view and short axis) showed an aneurysmal defect (arrow) and the electrocardiogram left axis deviation and a right bundle branch block. RV, right ventricle; LV, left ventricle; RA, right atrium; LA, left atrium; VSD, ventricular septal defect; AD, aneurysmal defect; AO, aorta; T, tricuspid valve.

significantly influence the QRS axis. But the extreme left QRS axis deviation in our patients cannot be attributed to a great left ventricular enlargement because most of these patients had normal electrocardiograms and few showed only a slight or moderate left ventricular enlargement. Also one of our patients had banding of the pulmonary artery in infancy because of a large ventricular septal defect and heart failure. Some years later angiography showed spontaneous closure of the ventricular septal defect (fig 5) with an aneurysm of the membranous septum and systemic pressure in the right ventricle. The electrocardiogram showed right ventricular hypertrophy and left axis deviation.

Since the case described by Laennec in 1826, (cited by Freedom *et al* [6]), there have been many reports of aneurysms of the membranous septum,[15-17] and the association with many congenital cardiac anomalies, arrhythmias,[18-20] and conduction defects has been established.[18 20 21] But an association with an extreme left axis deviation has not been mentioned.

Freedom *et al* did not find features in the electrocardiogram that distinguished between ventricular septal defect with an associated aneurysm of the membranous septum (seen

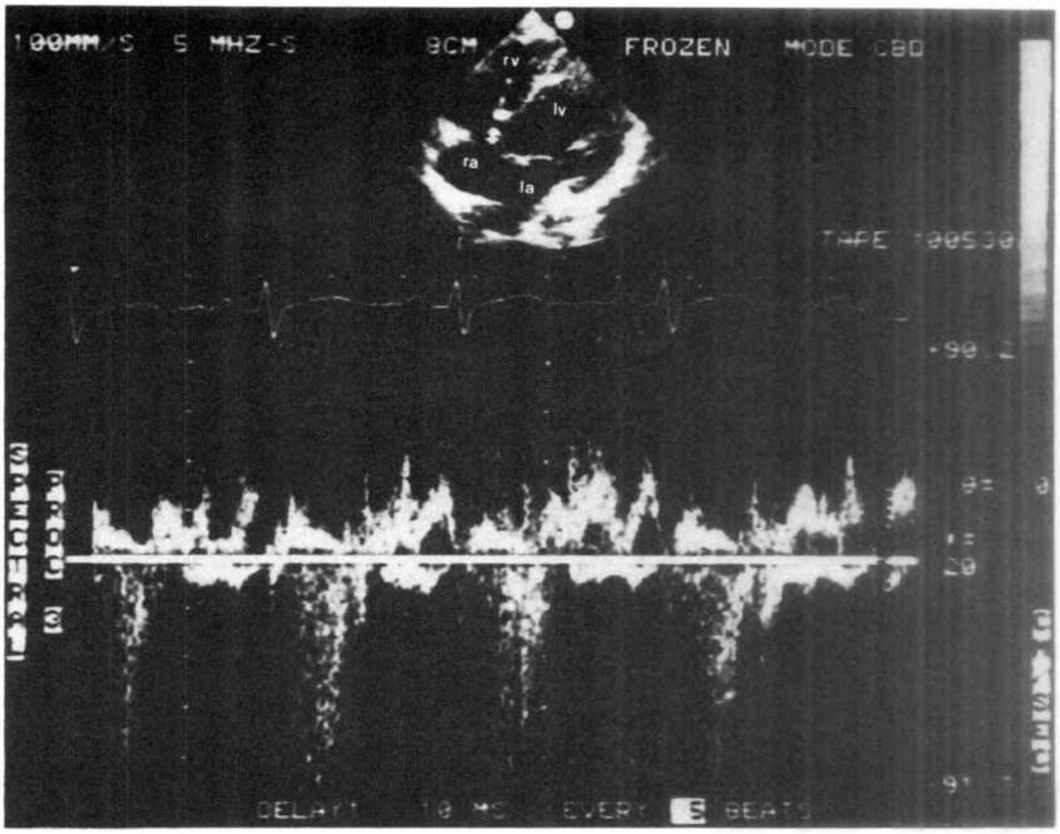

Figure 4 Cross sectional and Doppler echocardiograms in a patient with a perimembranous ventricular septal defect, aneurysmal defect and left axis deviation. There was mild to moderate tricuspid insufficiency. RV, right ventricle; LV, left ventricle; RA, right atrium; LA, left atrium.

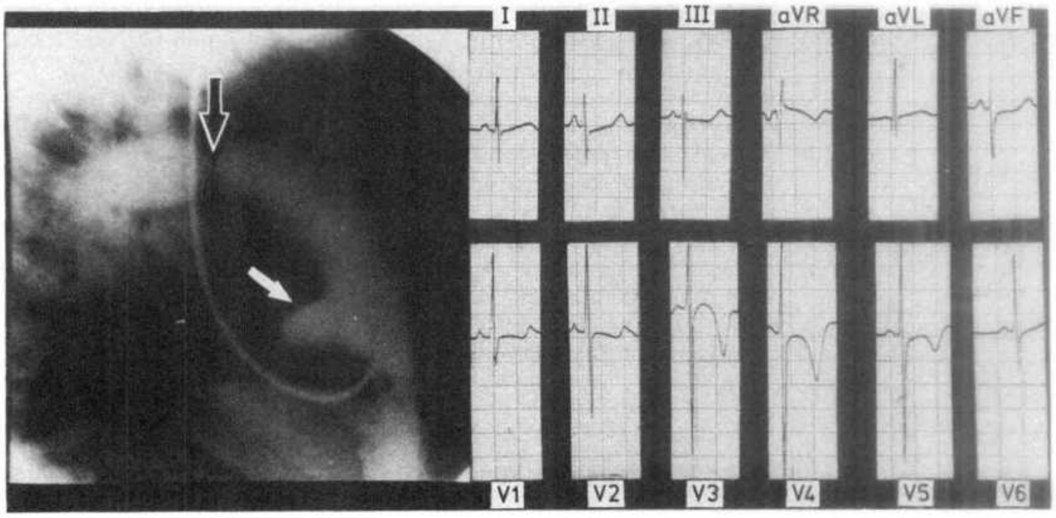

Figure 5 Lateral right ventricular angiogram and electrocardiogram showing the aneurysmal pouch protruding into the left ventricle without shunting (solid arrow)—contrast medium did not enter the left ventricle—and tight banding of the pulmonary artery (open arrow). The electrocardiogram showed left axis deviation and right ventricular overload.

angiocardiographically) and an isolated membranous defect. Only four (7%) of their 56 patients had a frontal plane axis of $-15°$ to $-60°$; two of them had an aneurysm.[6]

So far angiocardiography has been the only means of diagnosing aneurysms of the membranous septum.[6 9 10] But patients with small ventricular septal defect do not generally need angiocardiography and should be managed clinically. The incidence of such aneurysms of the membranous septum is therefore unknown, though it was thought to be high.[6 9 10]

Today the non-invasive technique of echocardiography can easily confirm the presence of aneurysms of the membranous septum associated with perimembranous ventricuar septal defects and follow them through the years.[22-24] We found that the short axis and apical four chamber views were the most helpful in visualising the area of the membranous septum. An aneurysm of the membranous septum is often found at echocardiography[24] in patients with a perimembranous ventricular septal defect but the high frequency of an extreme deviation of the left axis in our patients is surprising. We believe that spontaneous closure of ventricular septal defect can be anticipated if the defect becomes smaller and a left axis deviation appears.

We think that far from being an indication for invasive studies the development of left axis deviation in patients with small ventricular septal defects forecasts the spontaneous reduction of the defect by apposition of the septal tricuspid valve leaflet and by an aneurysm of the membranous septum. Such patients only need careful clinical management even if the venticular septal defect is large and seems to need surgical closure.

Bäckman found that 7·8% of his patients with left axis deviation also had incomplete right bundle branch block.[1] We found that half of our patients with left axis deviation also had right bundle branch block.

There have been several reviews of the anatomical relation of aneurysms of the membranous septum to the tricuspid valve.[13,15,25] They suggested that dysfunction of the tricuspid valve was likely because it was affected by the aneurysm of the membranous septum. Freedom *et al* reported angiographc evidence of tricuspid insufficiency in four patients with aneurysms of membranous septum. They also suggested that an aneurysm can cause tricuspid insufficiency, perhaps by deforming the overlying septal leaflet.[6] Others reported the same association.[17,26,27] This dysfunction may explain the tricuspid insufficiency found in all seven patients that we studied by Doppler echocardiography.

At auscultation tricuspid valve dysfunction may be masked by the features of the associated ventricular septal defect.

The apposition of the septal tricuspid valve leaflet and the aneurysm of the membranous septum that we found in two thirds of patients aged under two years accords with the clinical observation that most of the ventricular septal defects that become smaller or close spontaneously do so before the patient reaches the age of two.[3,6,28] Freedom *et al* pointed out that aneurysms are not unique, as was thought, to children aged more than two; they found clinical, angiographic, and anatomical evidence of this feature in infants.[6]

We still do not know the anatomical basis for the development of extreme left axis deviation when the septal tricuspid valve leaflet adheres to the rim of the septal defect and whether this deviation is transient or permanent.

1 Backman H. Influence of structural and functional features of ventricular septal defect on frontal plane QRS axis of the electrocardiogram. *Br Heart J* 1972,34:274–83.

2 Agustsson MH, Arcilla RA, Bicoff JP, Moncada R, Gasul BM Spontaneous functional closure of ventricular septal defects in fourteen children demonstrated by serial cardiac catheterizations and angiocardiography. *Pediatrics* 1963; 31:958–68

3 Hoffman JIE, Rudolph AM. The natural history of ventricular septal defect in infancy. *Am J Cardiol* 1965; 16:634–53.

4 Campbell M. Natural history of ventricular septal defect. *Br Heart J* 1971;33:246–57.

5 Varghese PJ, Izukawa T, Celermajer J, Simon A, Rowe RD. Aneurysm of the membranous ventricular septum: a method of spontaneous closure of small ventricular septal defect. *Am J Cardiol* 1969;24:531–6.

6 Freedom RM, White RD, Pieroni DR, Varghese PJ, Krovetz LJ, Rowe RD. The natural history of the so-called aneurysm of the membranous ventricular septal defect. *Circulation* 1974;49·375–84.

7 Steinberg I. Diagnosis of congenital aneurysm of the ventricular septum during life. *Br Heart J* 1957;19:8–12.

8 Edelstein J, Charms BL. Ventricular septal aneurysm. *Circulation* 1965;32:981–4.

9 Beerman LB, Park SC, Fisher DR, *et al.* Ventricular septal defect associated with aneurysm of the membranous septum. *J Am Coll Cardiol* 1985;5:118–23.

10 Nugent EW, Freedom RM, Rowe RD, Wagner HR, Rees JK. Aneurysm of the membranous septum in ventricular septal defect. *Circulation* 1977;56(suppl I):82–4.

11 Albers HJ, Carroll SE, Coles JC. Spontaneous closure of a membranous ventricular septal defect. *Br Med J* 1962, iii:1162–3.

12 Bloomfield DK The natural history of ventricular septal defect in patients surviving infancy. *Circulation* 1964, 29:914–55.

13 Anderson RH, Lenox CC, Züberbühler JR. Mechanism of closure of perimembranous ventricular septal defect. *Am J Cardiol* 1983;52:341–5.

14 Gup AM, Franklin RB, Hill JE. The vectorcardiogram in children with left axis deviation and no apparent heart disease. *Am Heart J* 1965;69:619–23.

15 Baron MG, Wolf BS, Grishman A, Van Mierop LHS. Aneurysm of the membranous septum. *Am J Roentgenol* 1964;91:1303–14.

16 Jain AC, Rosenthal R. Aneurysm of the membranous ventricular septum *Br Heart J* 1967,29:60–3.

17 Chesler E, Korns ME, Edwards JE. Anomalies of the tricuspid valve, including pouches, resembling aneurysms of the membranous ventricular septum. *Am J Cardiol* 1968;21.661–8.

18 Clark RJ, White PD. Congenital aneurysmal defect of the membranous portion of the ventricular septum associated with heart block, ventricular flutter, Adams-Stokes syndrome and death. *Circulation* 1952;5:725–9.

19 Larsen KA, Noer T. Cardiac aneurysm of the membranous portion of the interventricular septum. *Acta Med Scand* 1960;166:401–5.

20 Heggtveit HA. Congenital aneurysm of the membranous septum associated with bundle branch block. *Am J Cardiol* 1964;14:112–7.

21 Shumacker HB, Glover J. Congenital aneurysm of the ventricular septum. *Am Heart J* 1963;66:405–8.

22 Snider AR, Silverman NH, Schiller NB, Ports TA. Echocardiographic evaluation of ventricular septal aneurysms. *Circulation* 1979;59.920–6.

23 Canale JM, Sahn DJ, Valdes-Cruz LM, Allen HD, Goldberg SJ, Ovitt TW. Accuracy of two-dimensional echocardiography in the detection of aneurysms of the ventricular septum. *Am Heart J* 1981;101 255–9.

24 Ramaciotti C, Keren A, Silverman NH. Importance of (perimembranous) ventricular septal aneurysm in the natural history of isolated perimembranous septal defect. *Am J Cardiol* 1986;57:268–72.

25 Tandom R, Edwards JE Aneurysmlike formation in relation to membranous ventricular septum. *Circulation* 1973;47: 1089–97.

26 Pombo E, Pilapil VR, Lehan PH Aneurysm of the membranous ventricular septum. *Am Heart J* 1970;79:188–93.

27 Eshaghpour E, Kawai N, Linhart JW. Tricuspid insufficiency associated with aneurysm of the ventricular septum. *Pediatrics* 1978;61:586–92.

28 Hoffman JIE, Rudolph AM. The natural history of isolated ventricular septal defect. *Adv Pediatr* 1970;17:57–79.

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Use of balloon dilatation to treat supravalvar pulmonary stenosis developing after anatomical correction for complete transposition

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Abstract

Eight balloon dilatations were performed in five patients (aged from 10 to 37 months) in whom supravalvar pulmonary stenosis developed after anatomical correction for complete transposition. The ratio of the maximum diameter of the inflated balloon to the narrowest pulmonary arterial diameter varied from 1·6 to 3·3. In three patients with an initial ratio of ≤2 dilatation was repeated with a larger balloon. The right ventricular systolic pressure ranged from 0·70 to 1·25 of the simultaneously measured femoral arterial systolic pressure. The major stenosis was in the main pulmonary artery in four patients and at the pulmonary arterial bifurcation in one. After balloon angioplasty in the four patients there was no significant improvement in the ratio of right ventricular to femoral arterial systolic pressure or in the angiographic appearance. There was no change in the pressure ratio after angioplasty in the patient who had a major stenosis of the pulmonary arterial bifurcation and mild main pulmonary artery narrowing. There seemed to be a slight angiographic improvement in the bifurcation stenosis but at restudy two months later the angiographic improvement had disappeared.

Balloon angioplasty of supravalvar pulmonary stenosis developing after anatomical correction for complete transposition was not successful in eight procedures. This lack of success may be attributable to a small pulmonary annulus with consequent multiple levels of stenosis and distortion of the main pulmonary artery.

Over the past few years balloon dilatation procedures have been increasingly used to treat various congenital heart defects. When they are successful major cardiac operation can be avoided or delayed. Balloon dilatation is now an established treatment for certain defects such as pulmonary valve stenosis or recoarctation. Its value in other conditions such as native coarctation or pulmonary vein stenosis remains controversial.[1] We performed balloon dilatation in five patients in whom supravalvar pulmonary stenosis developed after anatomical correction for complete transposition of the great arteries.

Patients and methods

Balloon dilatation of supravalvar pulmonary stenosis after the anatomical correction for complete transposition was attempted in eight patients. In three patients it could not be successfully undertaken because the stenotic segment could not be crossed with the balloon. Two of these patients had bilateral ileofemoral venous thrombosis, and successful balloon catheter manipulation could not be achieved from the internal jugular vein. The remaining five patients underwent balloon dilatation. In three of the five patients the dilatation was later repeated with a larger balloon; there were eight dilatation procedures in total.

The five patients were boys who were aged 10 to 37 months (median 15 months) at the time of balloon dilatation. Anatomical correction for complete transposition had been performed 7–17 days after birth. During operation autologous pericardium was used to augment the new pulmonary artery anastomosis in two patients. Preserved bovine pericardium was used in the other three patients. There were no other cardiac abnormalities except a small mid-muscular ventricular septal defect in one patient. This was closed at surgical correction.

Each patient had clinical, electrocardiographic, and echocardiographic findings typical of considerable supravalvar pulmonary stenosis. Cardiac catheterisation was performed under general anaesthesia. A decision to undertake balloon angioplasty was made if (*a*) the right ventricular systolic pressure exceeded 66% of the femoral arterial systolic pressure and (*b*) angiography showed a considerably narrowed segment in the supravalvar region of the right ventricular outflow tract.

The internal diameters of the narrowest segment and the pulmonary annulus were measured from selected right ventricular angiographic images. These measurements were taken from cinevideo images and corrected for magnification with a 1 cm grid recorded in the approximate position of the patient's right ventricular outflow tract. A balloon diameter of 2–3 times the diameter of the narrowest segment and not exceeding 1·3 times the pulmonary annulus diameter was chosen. The stenotic segment was crossed initially with an end hole catheter and a J tip Teflon coated exchange guide wire positioned in a peripheral pulmonary artery. A balloon angioplasty catheter (Medi-tech, Mansfield

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Table 1 Data from cardiac catheterisation and angiocardiography

Patients	*Age at dilatation (mnth)*	*Major stenosis*	*PV annulus diameter (mm)*	*Narrowest diameter (mm)*	*Balloon diameter (mm)*	*Ratio of balloon to narrowest diameter*
1a	19	MPA	9·5	5·0	8	1·6
b	22	MPA	9·8	5·5	12	2·2
2a	12	MPA	9·0	4·0	7	1·7
b	15	MPA	9·0	4·4	10	2·3
3	37	MPA	11·5	7·0	13	1·8
4	10	MPA	9·0	6·0	12	2·0
5a	10	LPA	11·0	3·0	6	2·0
		RPA		4·8		
b	12	LPA	11·0	3·0	10	3·3
		RPA		5·0		

LPA, left pulmonary artery; MPA, main pulmonary artery; PV, pulmonary valve; RPA, right pulmonary artery.

Table 2 Results of balloon dilatation

	Before dilatation			*After dilatation*		
Patient	*RV/FA pressure ratio*	*PA to RV gradient (mm Hg)*	*Narrowest diameter (mm)*	*RV/FA pressure ratio*	*PA to RV gradient (mm Hg)*	*Narrowest diameter (mm)*
1a	0·70	50	5·0	0·80	50	5·0
b	0·85	60	5·5	0·95	60	5·5
2a	1·25	80	4·0	1·15	70	4·0
b	0·90	60	4·4	0·90	55	4·4
3	0·70	55	7·0	0·70	50	7·2
4	0·70	38	6·0	0·80	40	6·0
5a	0·95	70	3·0 (LPA)	0·90	70	3·5 (LPA)
			4·8 (RPA)			4·8 (RPA)
b	0·90	65	3·0 (LPA)	1·10	70	3·0 (LPA)
			5·0 (RPA)			5·2 (RPA)

FA, femoral artery; LPA, left pulmonary artery; PA, pulmonary artery; RPA, right pulmonary artery; RV, right ventricle.

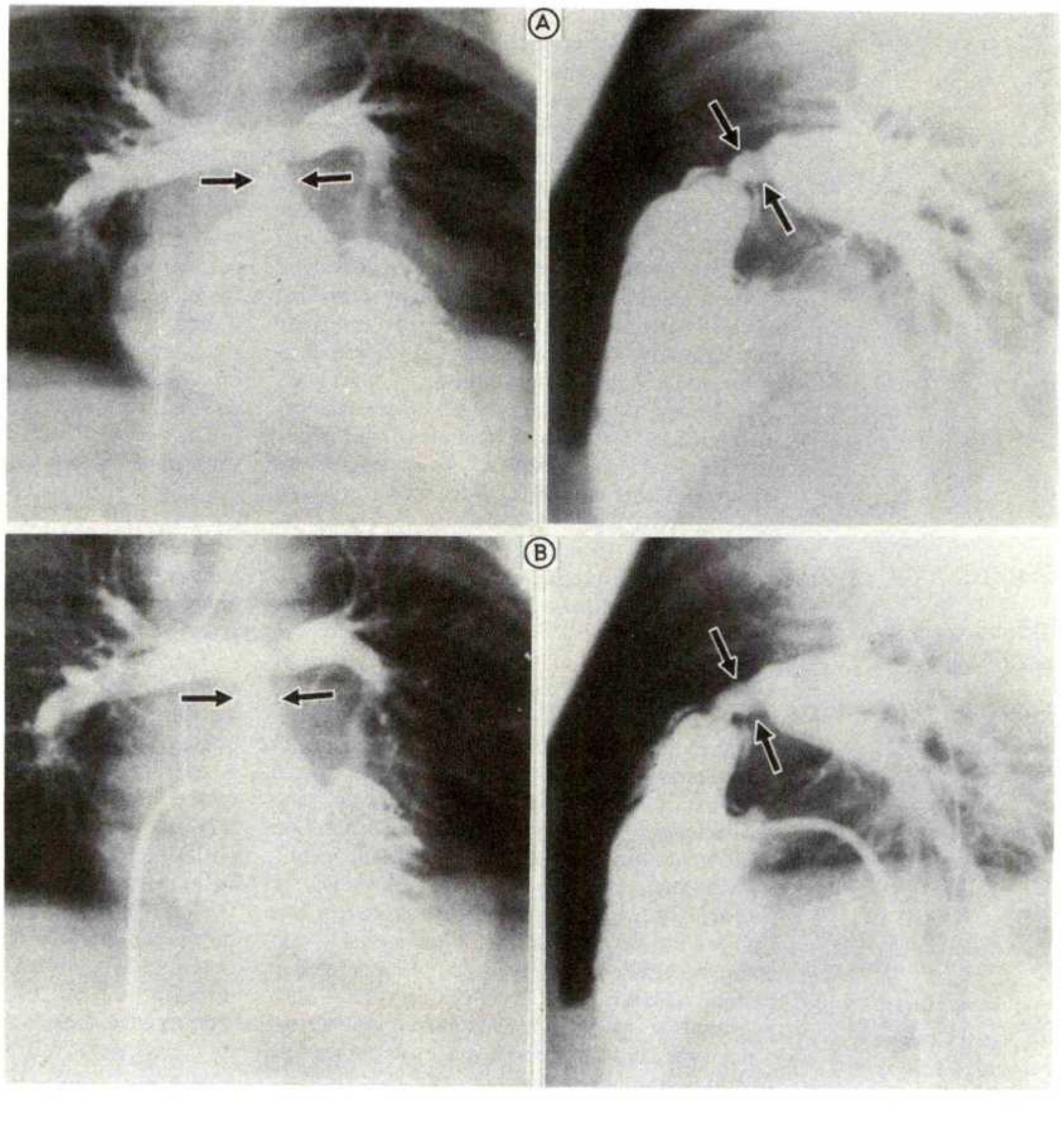

Figure 1 Anteroposterior and lateral views of a right ventriculogram showing supravalvar pulmonary stenosis with hypoplasia of the pulmonary trunk (arrows) before (A) and after (B) balloon dilatation.

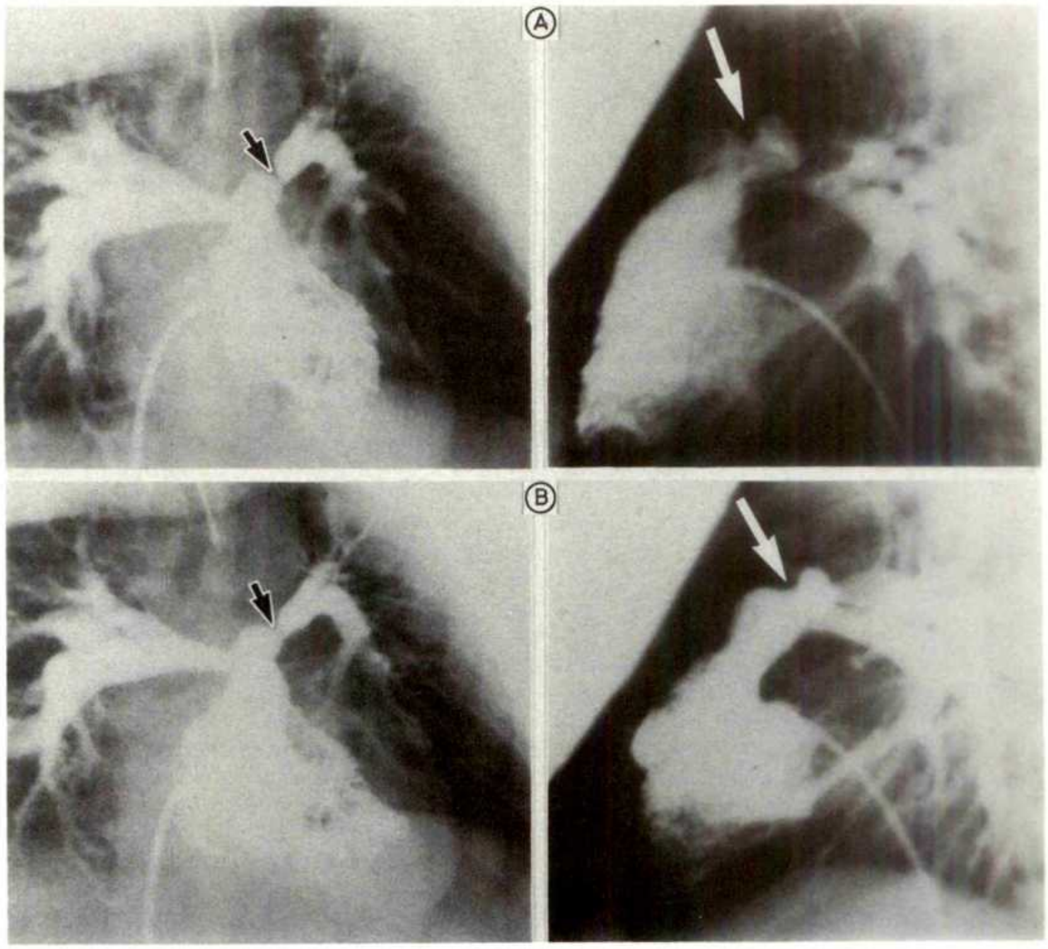

Figure 2 Anteroposterior and lateral views of a right ventriculogram showing bifurcation stenosis, a particularly severe stenosis at the origin of the left pulmonary artery (small arrow), and mild supravalvar pulmonary stenosis (big arrow) before (A) and after (B) balloon dilatation.

Scientific or Schneider Medintag) was guided across the stenotic segment. The balloon was inflated with one quarter strength contrast solution at the manufacturer's recommended pressure (usually 4–6 atmospheres) by a SciMed inflation device. It was inflated for 15 to 30 seconds under electrocardiographic and femoral arterial pressure monitoring and four dilatations were performed at each stenotic site. Only one patient required dilatation at two sites of narrowing (table 1).

After balloon dilatation repeat right ventricular and femoral arterial systolic pressures were recorded simultaneously. A right ventriculogram was obtained under the same conditions as the predilatation angiogram. The angioplasty was regarded as successful if (*a*) there was a fall in right ventricular systolic pressure to $<50\%$ of femoral arterial systolic pressure or (*b*) there was an improvement of $>50\%$ in the measured diameter of the narrowest segment on angiography or both. The angioplasty was also considered successful if these criteria were fulfilled on a follow up cardiac catheterisation, which was undertaken in three patients.

Results

All patients had moderate to severe supravalvar pulmonary stenosis on cardiac catheterisation. The right ventricular systolic pressure before dilatation ranged from 50 to 95 mm Hg and this was 70–125% of the simultaneous femoral arterial systolic pressure. The pulmonary arterial pressure beyond the stenotic segment was normal in all patients. The subsequent gradient across the right ventricular outflow tract obstruction varied from 38 to 80 mm Hg and was not reduced by dilatation (table 2).

In four patients the anastomotic segment was stenosed in the main pulmonary artery close to the pulmonary valve and in two it restricted the pulmonary valvar leaflets. This stenotic segment was not discrete and the distal main pulmonary artery also showed varying degrees of tubular hypoplasia. Therefore the diameter of the normal portion of the pulmonary artery distal to the site of obstruction could not be determined. In the fifth patient there was a slight stenosis in the main pulmonary artery but the origins of both the right and left pulmonary arteries were severely narrowed. Distal to the mild narrowing in the main pulmonary artery the pulmonary artery was 11·5 mm in diameter. The diameters of the left pulmonary artery and right pulmonary artery distal to severe bifurcation stenosis were 8 and 8·2 mm respectively.

Although the ratio of the selected balloon diameter to the diameter of the narrowest segment measured on cinevideo images at cardiac catheterisation was 2·0–3·0, remeasurement of the processed cineangiogram showed a ratio of 1·6–3·3 (median 2·0) (table 1). Three patients with ratios of 1·6, 1·7, and 2·0 at initial angioplasty underwent repeat dilatation at a later date with a balloon with a larger diameter. There was a long segment indentation in the balloon outline on inflation. This disappeared on full inflation but recurred on deflation.

Table 2 summarises the results of balloon dilatation. The ratio of right ventricular to femoral arterial systolic pressure did not change significantly in any of the eight procedures. Three patients (cases 1, 2, and 5) were restudied 2–3 months later. In two there was no improvement in the pressure (patients 1 and 5). Repeat angioplasty with a larger balloon was also unsuccessful. The third patient had a minor improvement in the ratio (1·25 to 0·90) at restudy but this did not meet the criteria for successful angioplasty. A repeat dilatation with a larger balloon did not produce any further improvement. There was no angiographic improvement in the stenotic segment in four of the five patients (fig 1).

In the fifth patient with a predominant bifurcation stenosis there was no haemodynamic change but the angiogram seemed to show a slight improvement in the stenosis at the origin of the left pulmonary artery (fig 2). This diameter increased from 3·0 to 3·5 mm but on restudy two months later it measured 3·0 mm. A second dilatation with a larger balloon produced no haemodynamic or angiographic improvement. At surgical repair in this patient, tissue from the wall of the bifurcation stenosis showed extensive adventitial fibrosis with some disorganisation of elastic lamellae but intact intimal and serosal layers. This suggests that the balloon stretched the stenosis but did not disrupt it.

There were no complications in the eight procedures. Transient hypotension, bradycardia, and electrographic ST segment changes were often seen during balloon inflation.

Surgical relief of the supravalvar stenosis with patch insertion into the stenotic regions was later successful in patients 1 and 5. The other three patients continue to show appreciable obstruction of the ventricular outflow tract (echocardiographic Doppler gradients 40–60 mm Hg).

Discussion

Development of supravalvar pulmonary stenosis is the most common important complication after anatomical correction for complete transposition.[2-4] Published reports describe successful surgical relief of the supravalvar obstruction in most patients. Balloon angioplasty for this lesion has been reported in five patients with success in only one patient[5]; also three patients later required operation.

Balloon angioplasty has been successfully used to dilatate vascular obstructions. Intimal and medial disruption was shown on histological examination in successful experimental dilatation of aortic coarctation in lambs.[6] Good results from balloon dilatation were reported in human postoperative aortic coarctation and pulmonary artery stenosis.[7 8] We performed balloon angioplasty in five patients with appreciable supravalvar pulmonary stenosis after anatomical correction for complete transposition. One patient (case 5) had major stenosis at the pulmonary arterial bifurcation and differed from the others. The bifurcation stenosis may occur as a result of the distortion of the pulmonary arterial bifurcation when the central pulmonary arteries are mobilised for reanastomosis at anatomical correction. It is less likely to be relieved by balloon angioplasty.[4]

The failure of balloon angioplasty to relieve supravalvar pulmonary stenosis in any of our patients indicates an intrinsic difference between this abnormality and the other obstructions of aortic recoarctation and pulmonary artery stenosis. The difference could be related to the nature of the pericardial patch inserted in the new pulmonary artery after coronary excision. Tanned pericardium retracts producing supravalvar stenosis; some thought that the use of autologous pericardium would avoid this complication.[3] Autologous pericardium was used in two of the five patients in our series with supravalvar stenosis. Balloon dilatation was unsuccessful in these patients too.

In children with normal vessels the diameters of the pulmonary trunk and pulmonary annulus are greater than the diameter of the ascending aorta.[9] This discrepancy is greater in infants with complete transposition. The difference has been implicated in the development of supravalvar pulmonary stenosis after the anatomical correction.[10] The new pulmonary trunk and annulus are smaller and when there is also stenosis at the site of anastomosis and coronary excision, their size may contribute to the development of a hypoplastic segment in the supravalvar area rather than a discrete stenosis. This hypoplastic segment is less likely to be amenable to balloon angioplasty than a discrete stenosis.

In most patients with supravalvar stenosis after anatomical correction the stenotic segment lies close to the pulmonary valve. The diameter of the pulmonary annulus is therefore an important factor in the selection of the balloon because an oversized balloon may damage the pulmonary valve. Because the balloon lies across the pulmonary valve during dilatation it is difficult to keep it inflated for long periods without causing considerable haemodynamic deterioration, whereas in the peripheral pulmonary artery stenosis a balloon can be inflated for minutes.

Balloon angioplasty was not successful in any of the eight dilatation procedures attempted on five patients with supravalvar pulmonary stenosis developing after anatomical correction for complete transposition. These results were obtained despite the use of what we believed to be balloons of appropriate sizes (that is, compared with the size of the pulmonary valve annulus and the narrowest segment). Oversized balloons increase risk and there is little evidence that they are any more successful, particularly when this condition may be caused by multiple grades of stenosis within the same segment of vessel.

1 Perry SB, Keane JF, Lock JE. Interventional catheterisation in paediatric congenital and acquired heart disease. *Am J Cardiol* 1988;**61**(suppl):109–17.
2 Quaegebeur JM, Rohmer J, Ottenkamp J, *et al.* The arterial

switch operation—an eight year experience. *J Thorac Cardiovasc Surg* 1986;92:361–84.

3 Sidi D, Planche C, Kachaner J, *et al.* Anatomic correction of simple transposition of the great arteries in 50 neonates. *Circulation* 1987;75:429–35.

4 Wernovsky G, Hougen TJ, Walsh EP, *et al.* Midterm results after the arterial switch operation for transposition of the great arteries with intact ventricular septum: clinical, haemodynamic, echocardiographic and electrophysiologic data. *Circulation* 1988;77:1333–44.

5 Zeevi B, Keane JF, Perry SB, Lock JE. Balloon dilatation of postoperative right ventricular outflow obstructions. *J Am Coll Cardiol* 1989;14:401–8.

6 Lock JE, Niemi T, Burke BA, Einzig S, Castaneda-Zuniga WR. Transcutaneous angioplasty of experimental aortic coarctation. *Circulation* 1982;66:1280–6.

7 Saul JP, Keane JF, Fellows KE, Lock JE. Balloon dilatation angioplasty of postoperative aortic obstructions. *Am J Cardiol* 1987;59:943–8.

8 Lock JE, Castaneda-Zuniga WR, Fuhrman BP, Bass JL. Balloon dilatation angioplasty of hypoplastic and stenotic pulmonary arteries. *Circulation* 1983;67:962–7.

9 de la Cruz MV, Anselmi G, Romero A, Monroy G. A qualitative and quantitative study of the ventricles and great vessels of normal children. *Am Heart J* 1960;60:675–90.

10 Bical O, Hazan E, LeCompte Y, *et al.* Anatomic correction of transposition of the great arteries associated with ventricular septal defect: midterm results in 50 patients. *Circulation* 1984;70:891–7.

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Idiopathic infantile arterial calcification in two siblings: failure of treatment with diphosphonate

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Abstract

Two siblings with idiopathic infantile arterial calcification are reported. The fetal and postnatal echocardiographic features were a large pericardial effusion, thickened pulmonary and aortic valves, poor pulsation of the descending aorta, and calcification of the great vessels. In one patient calcification was first detected at 33 weeks' gestation. Despite treatment with disodium etidronate both children died.

Idiopathic infantile arterial calcification is a rare congenital disorder that is usually fatal in the first six months of life. It is characterised by widespread fibrous proliferation in elastic and muscular arteries and is associated with areas of patchy calcification of elastic tissue. Myocardial ischaemia resulting in refractory cardiac failure is the usual cause of death. We report two siblings with this disorder; in one the diagnosis was made by fetal echocardiography. Both children died despite treatment with diphosphonate.

Case reports

PATIENT 1

This was the first child of unrelated teenage parents. The pregnancy was complicated by hydramnios and hypertension at 34 weeks. Spontaneous labour developed at 35 weeks and despite intravenous salbutamol a 2580 g girl was delivered vaginally one week later. Within a few hours she became tachypnoeic and required oxygen for cyanosis. On examination she had biventricular hypertrophy, heart sounds were single, and there was a grade 2/6 pulmonary ejection murmur. Only the femoral and axillary pulses were palpable and examination of the abdomen showed firm 4 cm hepatomegaly and 3 cm splenomegaly. The chest *x* ray showed cardiomegaly with normal pulmonary vascularity and the electrocardiogram was normal. A cross sectional echocardiogram showed normal cardiac connections with a large pericardial effusion and dense echoes reflected from the pulmonary and aortic valves. In addition, echocardiographic examination of the descending aorta showed very poor vessel pulsation. At cardiac catheterisation there was pulmonary hypertension but no stenosis of the pulmonary or aortic valves. When pulmonary artery calcification was seen on fluoroscopy the chest *x* ray was reviewed and linear calcification was detected in both axillary arteries and the descending aorta. A biopsy specimen of the posterior tibial artery showed calcium deposition within the internal elastic lamina and confirmed the diagnosis of idiopathic infantile arterial calcification. Further investigation showed a low plasma concentration of pyrophosphate (0·6 μmol/l (normal range in adults 1–6 μmol/l)) but other investigations including blood film; thyroid function tests; serum immunoglobulins; autoantibodies; TORCH (toxoplasma, rubella, cytomegalovirus, and herpes virus) screen; serum parathormone; plasma calcium, phosphate and magnesium; serum alkaline phosphatase; plasma cholesterol and triglycerides; liver function tests; urine aminoacids, mucopolysaccharides, and excretion of calcium and hydroxyprolene were all normal. Over the next 48 hours the infant required an exchange transfusion for haemolytic jaundice though there was no evidence of blood group incompatability or sepsis. After this, treatment with chlorothiazide and spironolactone was started and her cardiac failure and hepatosplenomegaly gradually regressed. Then treatment with disodium etidronate (20 mg three times a day) was started, and by four weeks of age her hepatosplenomegaly had resolved and she was gaining weight. At six weeks the dose of disodium etidronate was reduced to 11 mg three times a day and treatment with diuretics was stopped.

At 11 weeks she presented with screaming episodes (probably angina pectoris) and acute heart failure with electrocardiographic evidence of inferolateral myocardial ischaemia. Shortly after admission she suffered a cardiac arrest and resuscitation was unsuccessful. At necropsy the coronary arteries were grossly narrowed by widespread endarteritis and there was extensive calcium deposition between the muscular and subintimal layers.

PATIENT 2

Five years later the mother again became pregnant. Serial fetal echocardiography showed the development of a pericardial effusion and calcification of the great vessels by 33 weeks' gestation (fig 1). In view of the developing calcification and hydramnios, labour was induced at 35 weeks. When fetal distress developed an emergency caesarean section was carried out and a male infant (2680 g) was delivered. On examination both radial pulses were absent and the child was tachypnoeic. Chest and abdominal *x* rays

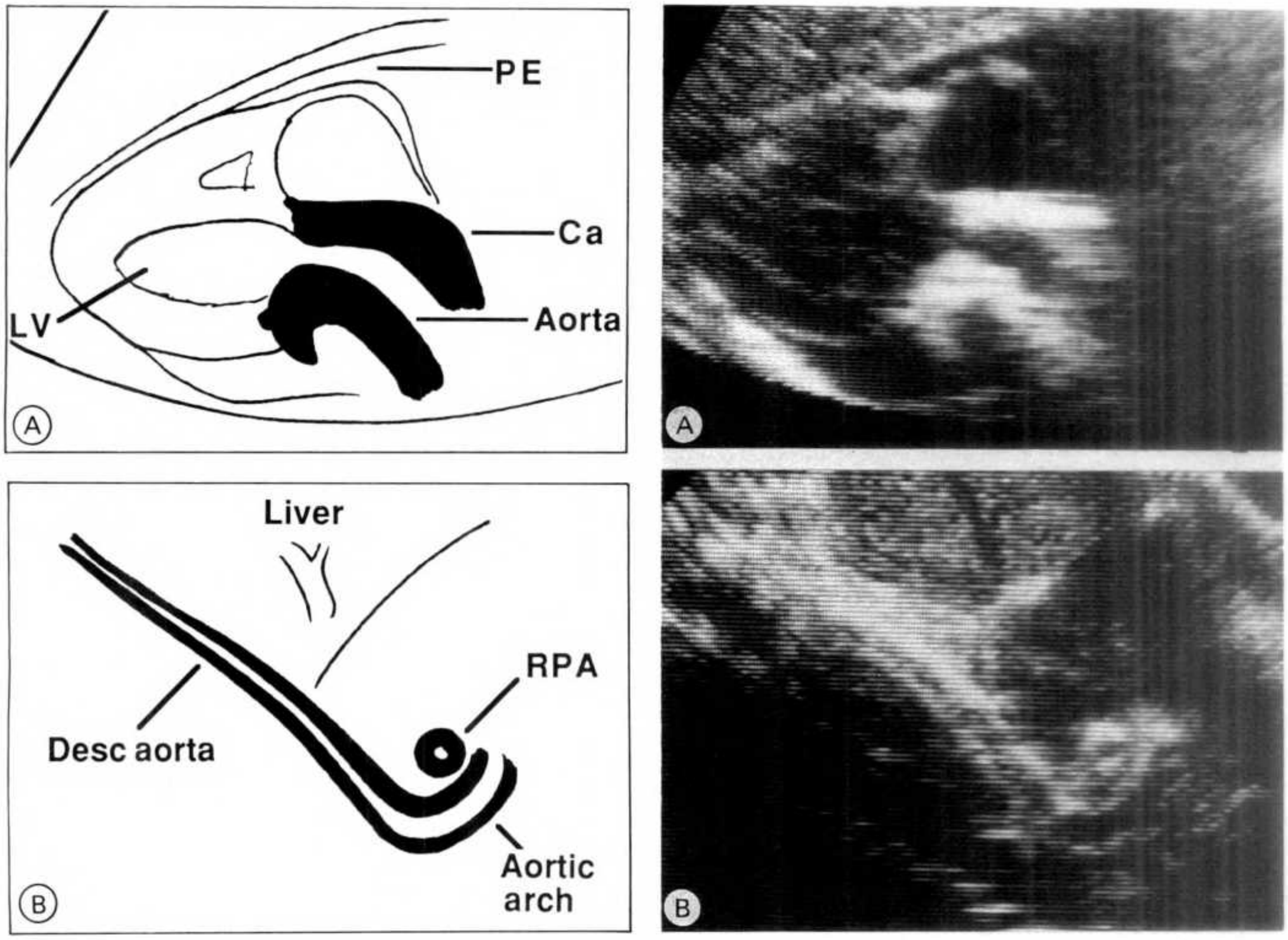

Figure 1 Fetal echocardiograms in patient 2 showing (A) calcification (Ca) of the ascending aorta and a pericardial effusion (PE). LV, left ventricle. (B) There was calcification of the aortic arch, descending aorta (Desc aorta), and right pulmonary artery (RPA).

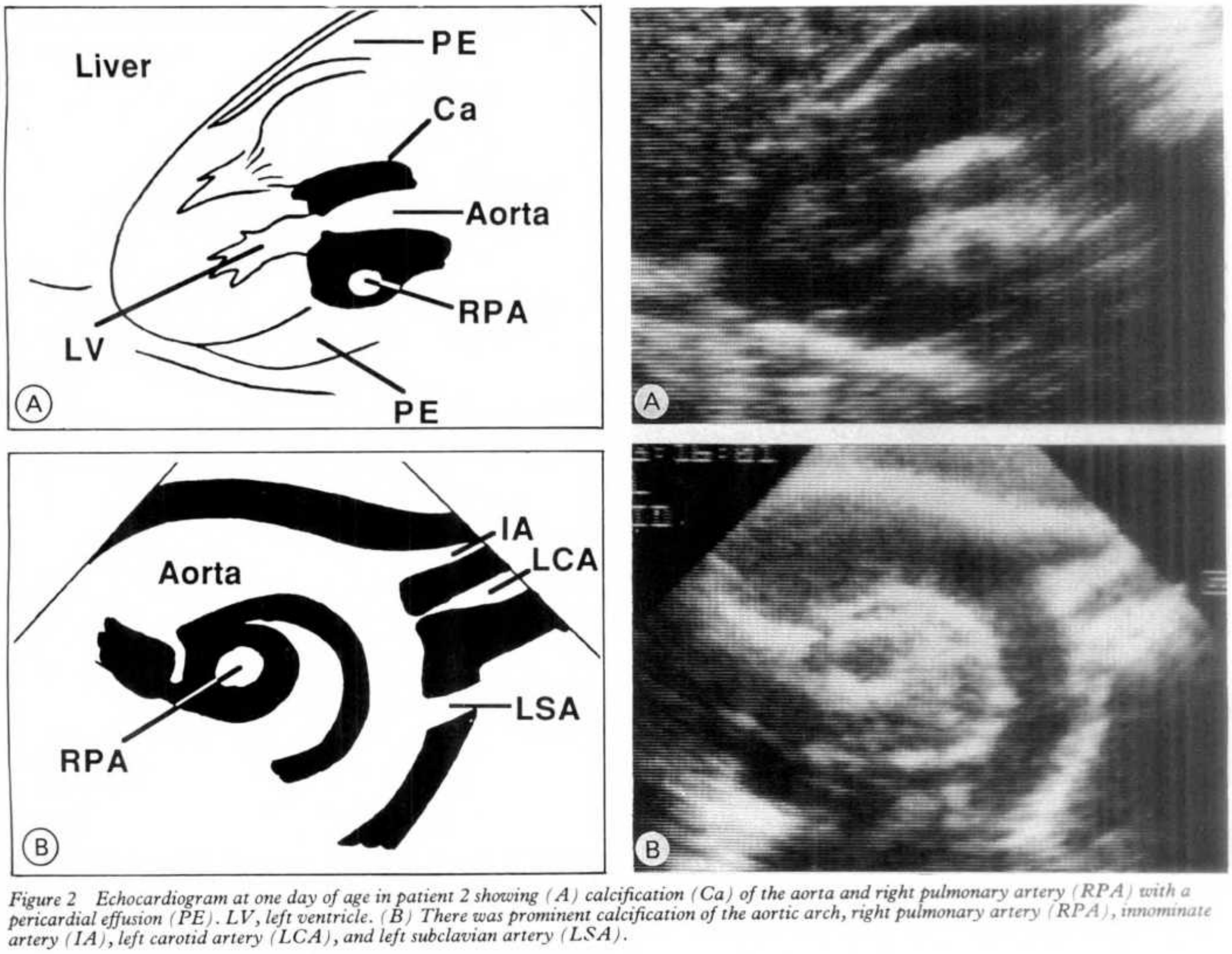

Figure 2 Echocardiogram at one day of age in patient 2 showing (A) calcification (Ca) of the aorta and right pulmonary artery (RPA) with a pericardial effusion (PE). LV, left ventricle. (B) There was prominent calcification of the aortic arch, right pulmonary artery (RPA), innominate artery (IA), left carotid artery (LCA), and left subclavian artery (LSA).

confirmed the presence of widespread arterial calcification. Cross sectional echocardiography showed that the heart was structurally normal but prominent calcification of the aorta and proximal pulmonary arteries was evident (fig 2). Further investigations including cranial ultrasound, plasma calcium and phosphate, serum alkaline phosphatase, serum creatinine, plasma electrolytes, serum albumin, and urine calcium and phosphate were normal. Treatment with disodium etidronate (20 mg three times a day), spironolactone, chlorothiazide, and digoxin was started. A thoracic computerised tomographic scan at three weeks showed calcification in both the thoracic and descending aorta. Five weeks later the child was readmitted in cardiac failure with clinical angina. There was electrocardiographic evidence of left ventricular hypertrophy with anterolateral ischaemia and despite treatment with glyceryl trinitrate and morphine his condition deteriorated. He died five days later. Permission for necropsy was refused.

Discussion

Idiopathic infantile arterial calcification is very rare. Its incidence is unknown but over 100 cases have been reported. Symptoms usually develop in the first few months of life although a few cases present in childhood or adolescence.[1,2] The sexes are equally represented and though it is not uncommon for siblings to be affected[3,4] the karyotype is usually normal. An autosomal recessive inheritance has been postulated.[4,5] Presentation in preterm infants is associated with a higher incidence of aortic calcification and a more severe form of the disease.[5,6]

Our patients presented with the typical nonspecific features of poor feeding, cyanosis, heart failure, lethargy, and respiratory distress. Clinical examination is often not helpful and the diagnosis is usually made by the recognition of arterial calcification on chest and abdominal *x* rays.[7] Soft tissue calcification (especially periarticular) is often an associated feature.[7,8] Peripheral pulses may be normal, absent, or weak and hypertension may be present.[8-10] The electrocardiogram is often normal but may show signs of left ventricular hypertrophy or myocardial ischaemia.[9,11] At cardiac catheterisation evidence of stiffness in the pulmonary and systemic artery walls, a low diastolic pressure, and a wide pulse pressure have been reported.[12] Aortography may show coronary artery occlusion or stenosis.[13] In many cases, however, the diagnosis is not made until after death.[11,14] The histopathological features include intimal fibrous proliferation in elastic and muscular arteries with elastic tissue degeneration and secondary calcification.[15] This intimal proliferation is thought to be the fundamental pathological change and Witzleben has suggested that "occlusive infantile arteriopathy" is a more appropriate term for the condition.[11]

Biochemical investigations are usually normal and there is no identifiable abnormality of calcium metabolism. In patient 1 the plasma concentration of pyrophosphate was lower than the normal adult range. Pyrophosphate is a potent inhibitor of calcification and it is possible that idiopathic infantile calcification is due to a deficiency of pyrophosphate. An alternative explanation is that the low pyrophosphate concentration is a secondary event related to calcium deposition. Others suggested that the underlying defect may be dystrophic calcification occurring in a previously injured arterial wall,[16] a disorder of iron metabolism,[3] or an inherited disorder of elastin structure.[9]

Antenatal diagnosis by fetal echocardiography has not been reported though Rosenbaum and Blumhagen noted striking acoustic shadowing of the aorta on abdominal ultrasound in a preterm infant.[17] In our second patient calcification was first detected at 33 weeks' gestation. If this is typical then diagnosis by fetal echocardiography may allow elective preterm delivery before the onset of cardiac failure but it will be too late for termination of pregnancy.

Although spontaneous regression and survival to adult life have been reported,[12,16] 85% of patients with idiopathic infantile arterial calcification die in the first six months of life.[15] Corticosteroids[18] and a combination of corticosteroids, thyroid hormone, and oestrogen[7] have been used to treat this condition with no convincing evidence of efficacy. Meradji *et al* used disodium etidronate and reported regression of calcification within a few weeks and complete and permanent disappearance by two years.[9] This compound is a diphosphonate used to treat metastatic calcification.[19] We used this compound in both our patients in a dose that is known rapidly to suppress bone turnover in adults. Despite this there was no objective improvement in the radiological and echocardiographic appearances and both children died. The patient described by Meradji had only mild coronary involvement and no signs of cardiac failure and may have had a milder variant of the condition. There has been no subsequent report of the successful use of diphosphonate in this condition.

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1 Rangaswami N, Chaudhar S, Flinn G, Sanyal S. Idiopathic linear calcification of the ascending aorta in an adolescent. *Am J Dis Child* 1979;**133**:860–1.
2 Moran JJ, Steiner GC. Idiopathic arterial calcification in a five year old child. A case report. *Am J Clin Pathol* 1962; **37**:521–6.
3 Moran JJ, Becker SM. Idiopathic arterial calcification of infancy. Report of two cases occurring in siblings and review of the literature. *Am J Clin Pathol* 1959;**31**:517–29.
4 Chen H, Fowler M, Cheng WY. Generalised arterial calcification of infancy in twins. *Birth Defects* 1982; **18**(3B):67–80.
5 Anderson KA, Burbach JA, Fenton LJ, Jaqua RA, Barlow JF. Idiopathic arterial calcification of infancy in newborn siblings with unusual light and electron microscopic manifestations. *Arch Pathol Lab Med* 1985;**109**:838–42.
6 Bacon JF. Arterial calcification in infancy. *JAMA* 1964; **188**:933–5.
7 Lussier-Lazaroff J, Fletcher BD. Idiopathic infantile

arterial calcification: roentgen diagnosis of a rare cause of coronary artery occlusion. *Pediatr Radiol* 1973;1·224–8.
8 Maayan Ch, Pelag O, Eyal F, Mogle P, Rosenmaan E, Bar Ziv J. Idiopathic infantile arterial calcification. a case report and review of the literature. *Eur J Pediatr* 1984; 142.211–5.
9 Meradji M, de Villeneuve VH, Huber J, de Bruijn WC, Pearse RG. Idiopathic infantile arterial calcification in siblings· radiologic diagnosis and successful treatment. *J Pediatr* 1978,92:401–5.
10 Milner LS, Heitner R, Thompson PD, *et al*. Hypertension as the major problem of idiopathic arterial calcification of infancy. *J Pediatr* 1984;105.934–8.
11 Witzleben CL Idiopathic infantile arterial calcification—a misnomer? *Am J Cardiol* 1970;26·305–9
12 Scholler GF, Yu JS, Bale PM, Hawker RE, Celermajer JM, Kozlowski K. Generalised arterial calcification of infancy: three case reports including spontaneous regression with long-term survival *J Pediatr* 1984,129:257–60
13 Retbi JM, Casasoprana A, Gabilan JC, Dehan M, Rosenstein-Retbi J. Idiopathic arterial calcification in infancy. *Eur J Pediatr* 1978,129:55–60.
14 Gower ND, Pinkerton JRH Idiopathic arterial calcification in infancy *Arch Dis Child* 1963;38·408–11
15 Moran JJ Idiopathic arterial calcification of infancy· a clinicopathological study *Pathol Ann* 1975;10 393–417
16 Marrott PK, Newcombe KD, Becroft DMO, Friedlander DH. Idiopathic infantile arterial calcification with survival to adult life *Pediatr Cardiol* 1984,5 119–22.
17 Rosenbaum DM, Blumhagen JD Sonographic recognition of idiopathic arterial calcification of infancy *Am J Radiol* 1986;146:249–50
18 Bickel E, Janssen W Arteriopathia calcificans infantum. *Arch Kinderheilk* 1963,169 274–85
19 Russell RGG, Smith R Diphosphonates: experimental and clinical aspects *J Bone Joint Surg* 1973,55B·66–86.

BRITISH CARDIAC SOCIETY NEWSLETTER

The Council of the British Cardiac Society has endorsed the suggestion for a regular newsletter in the journal. This will appear monthly, or at least in most issues. We hope that members will write to the president or to any of the council about matters of special interest or concern, views will be publicised in the newsletters whenever it seems appropriate to do so. But more important, the newsletter will give the officers of the society an opportunity of keeping members informed of recent discussion and decisions. In these difficult days we will have no shortage of topics.

The council will continue to guide the society in all matter of importance, but the committee structure will be enlarged and strengthened. The Joint Training and Manpower Group that was set up last year will liaise closely with the Specialist Advisory Committee—and indeed will have some members in common. The Audit Committee is also already in existence. Both of these bodies have representation from the Cardiology Committee of the Royal College of Physicians of London. We will also have groups with responsibility for data management, for liaison with technicians, and for public relations. Others may follow as and when the need arises. We will give more details in the next newsletter.

The meeting in Torquay seemed to go well, and it proved a popular venue. We are confident that Glasgow and Harrogate will be equally successful. The question now is whether or not members wish to have some meetings in London. We will be seeking your views.

Anxieties about staffing and training continue. We believe that the new proposals for training set out in the May issue of the journal and discussed at the business meeting in Torquay are important if we are to maintain standards that are comparable to the best in Europe. But at the time of writing we have not achieved final agreement with the Royal College of Physicians of London or with the Department of Health. In order to strengthen our case—especially with regard to registrars—we were asked by the college to provide up to date information on staffing levels at consultant and senior registrar level in time for a meeting of the Manpower Group in June. We accepted the importance of this, but it gave us a little over two weeks to conduct the 1990 biennial survey that was originally scheduled for July: previous surveys have taken up to a year for information to be completed. To compound our problem, the group at the University of Sussex who helped with previous surveys was not available on this occasion. Richard Vincent (now director of the Trafford Centre for Medical Research at the university) stepped into the breach, and together we had a fraught fortnight. We had a steep learning curve: we apologise to our many friends who may have felt harassed and who endured a number of procedural errors which would not have occurred were it not for the unseemly haste of the work. We are grateful for all the patient help that was given.

We must mention a small printers' error in the publication on the proposed pattern of future training that we failed to pick up at proof stage. The text referred to a period of three years after registration for general professional training: the table showed only two. The text, of course, was correct.

We have heard criticism that cardiologists have little enthusiasm for audit. We believe that we have led the field in this area. The pacemaker database was a pioneering effort, and the angioplasty register will be of comparable importance. Our own surveys of staffing and facilities are a type of audit, and our specialty was the first to conduct these. Some of the working parties set up by the society had a major component of audit (for example that on "Cardiology in the District Hospital"). The Joint Audit Committee of the Cardiology Committee of the Royal College of Physicians and the Society is now actively pursuing new areas of interest. It will examine the management of acute coronary disease initially as a pilot study in five district hospitals; a register is being set up to document complications of angiography also in a few centres at first but with plans for early expansion; visits by consultants have been arranged between departments in two regions—early experience in parts of South East Thames have proved rewarding and popular. Perhaps we have not been making enough noise about our activities, and perhaps our newsletters about our activities will help to correct this.

DOUGLAS CHAMBERLAIN
President, British Cardiac Society

NOTICES

British Cardiac Society
The Annual Meeting will take place at the Scottish Exhibition Centre, Glasgow on 30 April to 3 May 1991

Electricity and the heart
The 6th Einthoven Symposium will be held on 19 October 1990 in Leiden. The symposium, co-sponsored by the Netherlands Heart Foundation and the European Society for Cardiology, will be on electricity and the heart. Information from Mrs J Rust, Phia Berghoutlaan 21, 2343 PM Oegstgeest, The Netherlands. Telephone (+32) 71-17.35 53.

Br Heart J 1990;64:160–2

CASE REPORT

Pulmonary venous atrial obstruction after the Senning procedure: relief by catheter balloon dilatation

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Abstract

Pulmonary venous atrial stenosis developed after a modified Senning procedure in an infant with transposition of the great arteries. The pulmonary venous atrium was surgically revised, but the obstruction recurred. The stenosis was then enlarged by percutaneous balloon catheter dilatation. There was an immediate haemodynamic and echocardiographic improvement. Clinical and echocardiographic improvement persisted nine months after dilatation. The procedure was complicated by staphylococcal endarteritis.

Case report

A 16 month old female infant presented with dyspnoea. She was born with transposition of the great arteries and had a Senning procedure performed at the age of three months. Her pulmonary venous atrium was augmented with bovine pericardium. She did well until she was eight months old when pulmonary venous atrial obstruction rapidly appeared. Reoperation disclosed stenosis of the pulmonary venous atrium by neointimal tissue associated with the bovine pericardial patch. This tissue and the patch were resected, and the remaining defect was closed with native pericardium. Postoperatively, clinical and echocardiographic evaluation indicated resolution of the obstruction. Dyspnoea recurred when she was 16 months old and a new 3/6 continuous murmur was heard over the sternum. Cross sectional and Doppler echocardiography and cardiac catheterisation showed severe obstruction within the pulmonary venous atrium (table). Reoperation was considered, but our cardiovascular surgeons opted to try balloon dilatation of the obstruction. This approach was offered to the patient's parents as an alternative though untested treatment, and they gave their informed consent.

Haemodynamic and echocardiographic data

	One month before dilatation	*Immediately before dilatation*	*Immediately after dilatation*	*Five months after dilatation*
Mean PA (mm Hg)	22	22	18	—
Mean PAW (mm Hg)	21	18	12	—
Mean PVA upstream (mm Hg)	22	—	11	—
Mean PVA downstream (mm Hg)	—	5	7	—
RVEDP (mm Hg)	5	6	6	—
CI (l/min/m^2)	—	1·8	2·5	—
Max stenosis dimension by cross sectional echo (mm)	4	4	7	6
Max stenosis gradient by Doppler echo (mm Hg)	—	13	—	8

CI, cardiac index, mean of 6–7 thermodilution determinations; PA, pulmonary artery pressure; PAW, pulmonary artery wedge pressure, PVA, pulmonary venous atrium pressure, RVEDP, right ventricular end diastolic pressure.
Pressures grouped by time are representative of multiple samples and were generally not measured simultaneously.

The procedure was performed on 17 May 1989. The patient was 18 months old and she weighed 10·6 kg. The cardiac index was measured by the thermodilution technique (table). Right femoral arterial pressures were continuously monitored via the sidearm of a 6 F sheath. We used serial measurement of activated coagulation times (Hemochron, International Technidyne Corporation, Edison, NJ, USA) to assess heparinisation. A 3·6 F end hole catheter with a tip angled at approximately 90° (White preformed (renal) catheter, Becton, Dickinson and Company, Rutherford, NJ, USA) was positioned in the right ventricle. The tip of this catheter was turned to the patient's right, to direct a 0·018 inch flexible and steerable guide wire (Hi-Torque Floppy, Advanced Cardiovascular Systems, Temecula, Ca, USA) across the tricuspid valve into the pulmonary venous atrium. The catheter was advanced into the atrium, and the tip was turned posteriorly to direct the guide wire through the stenosis in the pulmonary venous atrium to the lower left pulmonary vein. The catheter was then advanced to this position. The guide wire was exchanged for a 0·021 inch guide wire, and the catheter was exchanged for an angiographic catheter. The pressure drop across the stenosis was measured (table) and pulmonary venous angiography was performed.

A 5F angioplasty catheter with a 5 mm diameter × 2 cm long balloon (polyethylene Dotter balloon dilatation catheter, Cook, Bloomington, In, USA) was advanced over the larger guide wire, purged with carbon dioxide, filled with dilute contrast material in the descending aorta, and positioned across the stenosis. Maximum balloon inflation produced no haemodynamic relief. Therefore, an identical catheter was similarly positioned across the stenosis via the left femoral artery.

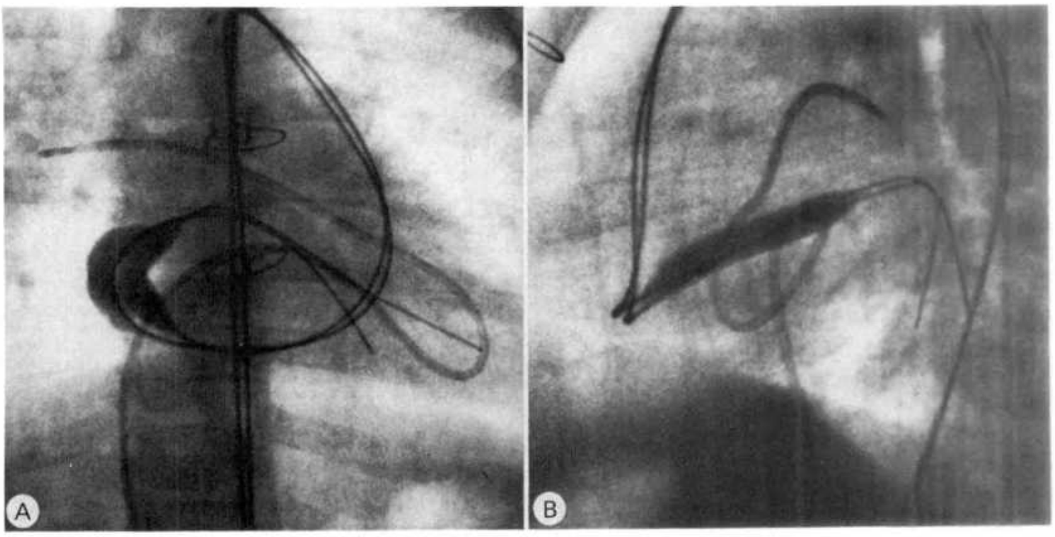

Figure 1 Two angioplasty balloons simultaneously inflated in the stenotic segment of the pulmonary venous atrium nearly abolishing the waist produced by the stenosis. A thermodilution catheter is positioned in the right pulmonary artery. (A) Posteroanterior and (B) lateral angiograms.

Because the left internal iliac artery was stenotic and would not accommodate a 6 F sheath, the second catheter was introduced directly through the skin. Four simultaneous double balloon inflations were performed (fig 1). The angioplasty balloon catheters were withdrawn and measurements of haemodynamic function (table) and pulmonary venous angiography (fig 2) were repeated before the end of the procedure.

The next day the patient was afebrile and seemed well. Her catheterisation wounds were clear and her femoral and pedal pulses were normal bilaterally. Cross sectional echocardiography showed relief of the stenosis in the pulmonary venous atrium (table). The patient was discharged from the hospital, but signs of infection in her left leg appeared over the next three days. She was readmitted to hospital with staphylococcal endarteritis of the left external iliac artery from which she recovered after a complicated course. Five months after the procedure, cross sectional and Doppler echocardiography showed persistent relief of the stenosis (table). Nine months after the procedure the patient remained symptom free.

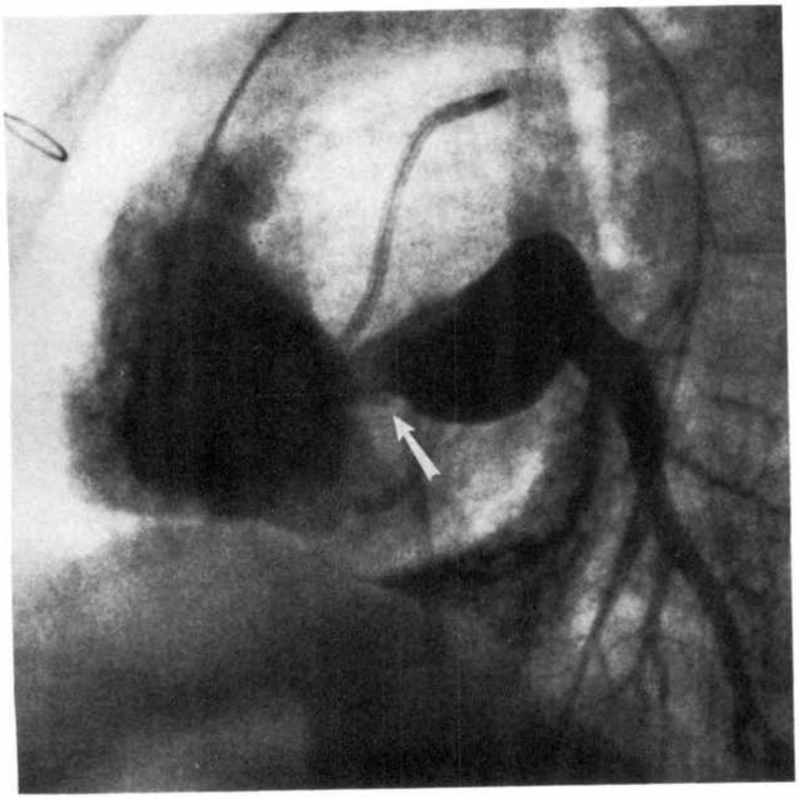

Figure 2 Lateral angiogram of the stenotic segment of the pulmonary venous atrium after balloon dilatation showing a tear in the inferior margin of the segment (arrow).

Discussion

It is important to select a balloon with a large enough diameter to dilate the stenosis. In our patient, the echocardiographic maximum dimension of the stenosis and its angiographic vertical extent were 4 mm. We chose to dilate the stenosis with 2–5 mm diameter balloons, the effective diameter of which was 8·2 mm.[1 2] This combination of balloons, the largest low profile balloons then available to us, did not fully abolish the stenosis.

However, the pressure drop was halved and the cardiac index increased. Furthermore, angiography showed a tear in the inferior wall of the stenosis, and echocardiography showed relief of the narrowing. Subsequent clinical and echocardiographic evaluations showed persistence of the improvement. A balloon diameter three to four times larger than the echocardiographically measured narrowest dimension of the pulmonary venous pathway obstructed after the Mustard operation was recommended for dilating such obstructions.[3] Thus larger balloons might have been more effective in our patient. Use of two small balloons seems preferable to a single large balloon technique because small balloons may be more easily manoeuvred through the systemic circulation, and the risk of mechanical injury to the femoral arteries or heart may be reduced.

After the procedure staphylococcal endarteritis and thrombosis developed in our patient's previously stenosed left external iliac artery. Ileofemoral arteriography showed a well developed collateral circulation to the left leg which may have masked the thrombosis initially. The artery was surgically explored, and thrombectomy was performed. Septic embolisation produced osteomyelitis in the femur, septic arthritis in the knee, and necrosis of part of the great toe. Neither endocarditis nor meningitis developed. This complication, unique in our experience and associated with no recognised technical mishap, indicates that risk of serious infection may be increased during complex and lengthy interventional catheterisations and that the use of prophylactic antibiotics should be considered.

Activated coagulation times were serially determined in the catheterisation laboratory to assess rapidly the patient's need for supplemental doses of heparin.[4 5] At the outset 100 units/kg of heparin was given. Six supplementary doses of 50 units/kg were given to maintain activated coagulation times of between 312 and 410 seconds. Guide wires remained within the systemic arterial circulation for several hours. However, only a trace of thrombus was seen on one of these wires when it was eventually withdrawn, and no other thrombus was seen during the procedure. Thus we believe that the activated coagulation time is a valuable measure of heparinisation during lengthy interventional catheterisations in infants and children.

Our experience reported in an infant with pulmonary venous atrial obstruction after a modified Senning procedure and that reported in children with similar stenoses after the Mustard operation[3] indicate that balloon catheter dilatation of these obstructions is a feasible alternative to reoperation.

1 Radtke W, Keane JF, Fellows KE, Lang P, Lock JE. Percutaneous balloon valvotomy of congenital pulmonary stenosis using oversized balloons *J Am Coll Cardiol* 1986; 8:909–15

2 Yeager SB. Balloon selection for double balloon valvotomy [Letter] *J Am Coll Cardiol* 1987;9·467–8.

3 Cooper SG, Sullivan ID, Bull C, Taylor JFN. Balloon dilatation of pulmonary venous pathway obstruction after Mustard repair for transposition of the great arteries. *J Am Coll Cardiol* 1989;14.194–8

4 Scott JA, Berenstein A, Blumenthal D. Use of the activated coagulation time as a measure of anticoagulation during interventional procedures *Radiology* 1986;158:849–50.

5 Ogilby JD, Kopelman HA, Klein LW, Agarwal JB. Adequate heparinization during PTCA· assessment using activated clotting time [Abstract]. *J Am Coll Cardiol* 1988;11.237A.

Br Heart J 1990;64:163–5

TECHNOLOGY

Percutaneous transcatheter myectomy of subvalvar pulmonary stenosis in tetralogy of Fallot: a new palliative technique with an atherectomy catheter

S A Qureshi, J M Parsons, M Tynan

Abstract

A male infant with tetralogy of Fallot was given a modified left Blalock-Taussig shunt at 11 days of age because of duct dependence. Twenty months later, because of increasing cyanosis and polycythaemia, he was given palliative treatment with balloon dilatation of the right ventricular outflow tract. Seven months later a right ventricular angiogram showed further progression of the infundibular stenosis with poor anterograde opacification of the pulmonary arteries. He underwent percutaneous transcatheter myectomy of the infundibulum with an atherectomy catheter. One month later he was well and less cyanosed.

Pulmonary atresia associated with the tetralogy of Fallot is usually congenital. Occasionally, atresia may develop at the infundibular level after a systemic to pulmonary artery shunt operation.[1 2] A valved conduit is sometimes required for complete repair in this situation which may then be associated with an increased morbidity and operative mortality.[1 3]

Although it is not possible to identify patients with tetralogy of Fallot who may develop pulmonary atresia, any intervention that prevents this complication may, ultimately, reduce the risks associated with complete surgical repair. Brock achieved effective palliation through closed infundibular resection or dilatation.[2 4 5] Similarly, balloon dilatation of the right ventricular outflow tract has recently been shown to be of value in infants and children with tetralogy of Fallot.[6 7]

We report the successful use of a new technique of transcatheter myectomy of the infundibulum in a child with tetralogy of Fallot.

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Case report

Tetralogy of Fallot was diagnosed in a one day old boy who weighed 2·5 kg. Cross sectional echocardiography showed confluent, but small, pulmonary arteries and severe pulmonary valvar and infundibular stenosis. When he was 11 days old he was given a modified (5 mm polytetrafluoroethylene) left Blalock-Taussig shunt because of severe cyanosis and dependence upon prostaglandin E_2 to maintain the patency of the ductus arteriosus.

At 14 months of age he was moderately cyanosed with a haemoglobin concentration of 19·3 g/l. Cardiac catheterisation showed that the pressure in the pulmonary artery (entered retrogradely through the shunt) was 10/0 (mean 8) mm Hg and the aortic pressure was 120/70 (mean 90) mm Hg. The aortic saturation was 81% in air. A right ventricular angiogram showed a trivial amount of contrast flowing through the infundibulum into the pulmonary trunk. The right ventricular outflow tract was dilated with a 5 mm balloon catheter and then a 8 mm balloon catheter. He was reinvestigated seven months later. Angiography showed severe infundibular stenosis. He underwent further balloon dilatation of the right ventricular outflow tract followed by transcatheter myectomy of the infundibulum with an atherectomy catheter.

Technique

Cardiac catheterisation was performed under general anaesthesia. The left femoral artery was cannulated with an 18 G Abbocath. Catheters were also introduced percutaneously into the right and left femoral veins. The right ventricular systolic pressure was 110 mm Hg, the femoral artery pressure 125/60 (mean 80) mm Hg, and the main pulmonary artery pressure 17/11 (mean 13) mm Hg. Saturations in the femoral artery were 78% and in the pulmonary artery 69%. A selective injection of contrast with the catheter in the infundibulum showed severe subvalvar pulmonary stenosis caused by hypertrophy of the infundibulum (fig 1). To allow an 8 French transseptal sheath (Bard International) to be passed into the pulmonary trunk, the outflow tract was dilated with an 8 mm diameter balloon catheter by the standard technique. The level of the infundibulum was marked with a needle positioned externally on the patient's chest. The 8 French

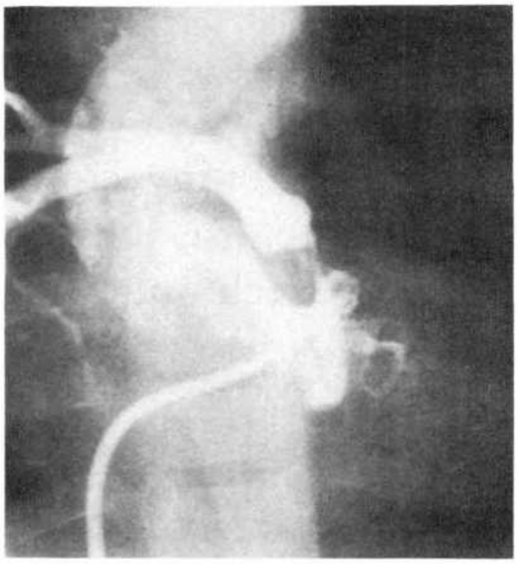

Figure 1 Selective angiogram in the infundibulum (anteroposterior projection) taken at start of procedure, showing gross hypertrophy of the infundibulum.

transseptal sheath and its dilator were advanced over an 0·035 inch guide wire and positioned in the proximal pulmonary trunk. The 6 French, Simpson coronary atherectomy catheter (Devices for Vascular Intervention) with a "nose cone" distal to the cutting window was prepared by purging the lumen port and 1·5 mm diameter balloon. The guide wire and the dilator were removed, leaving the sheath across the pulmonary valve. We introduced an 0·014 inch exchange guide wire through the sheath and advanced the atherectomy catheter over the wire until it was positioned across the infundibulum, using the landmarks from the marker needle. The sheath was then withdrawn and the catheter was rotated until the cutting window pointed postero-medially. The balloon was then fully inflated to a pressure of 4 atmospheres and the drill was activated by the motor drive unit and advanced manually (fig 2A). Nine cuts were made with the cutting window in different orientations. The balloon was deflated and the sheath advanced over the atherectomy catheter which was then removed. A further balloon dilatation with an 8 mm diameter balloon was then performed. All of the pieces of resected tissue were removed from the "nose cone". Microscopic examination confirmed that they were myocardium and fibrous tissue. A selective angiogram in the infundibulum showed a wider and irregular outflow tract (fig 2B). At the end of the procedure, the pressure was 16/7 (mean 10) mm Hg in the pulmonary artery, 125/80 (mean 100) mm Hg in the descending aorta, and 110 mm Hg in the right ventricle during systole. Oxygen saturation was 67% in the pulmonary artery and 81% in the descending aorta. There were no complications during or after the procedure. One month later he was well, less cyanosed, and the saturation by pulse oximetry was 85%.

Discussion

Many centres adopt a staged surgical approach in the treatment of tetralogy of Fallot.[3 8 9] This consists of the creation of a systemic to pulmonary artery shunt followed later by complete repair. This approach has the advantage of allowing continued growth of the pulmonary valve ring and pulmonary arteries, thus reducing the need for a transannular patch and decreasing the operative risk.[3] Occasionally, however, atresia may be developed at the

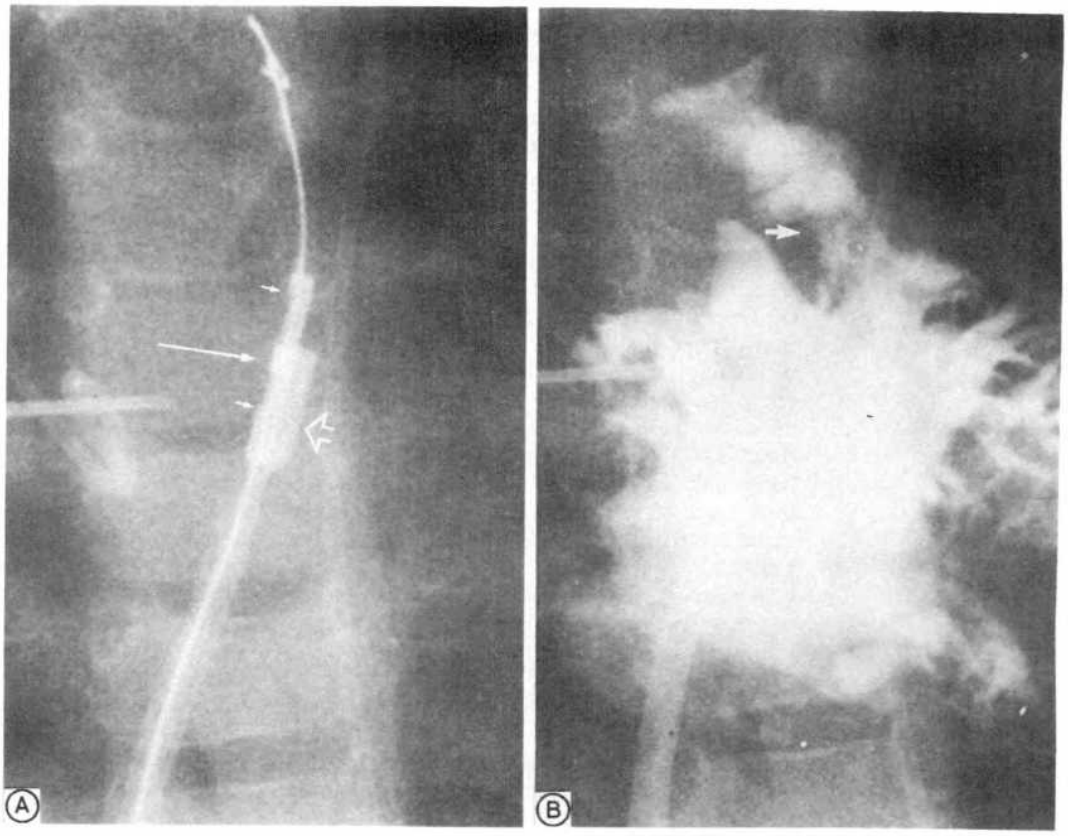

Figure 2 (A) Atherectomy catheter (on anteroposterior x ray screening) in position during myectomy. The balloon was inflated (hollow arrow), the cutting window (small arrows) was in contact with the infundibulum, and the drill, which was being advanced, can be seen (large arrow). (B) Selective angiogram in the infundibulum (anteroposterior projection) after myectomy. The outflow tract was wider and the surface of the infundibulum (arrow) was irregular.

infundibular level after a previous shunt operation.[1,2] Such a situation requires an extensive outflow patch or a conduit for complete repair.[1,3] Brock first reported the technique of infundibular resection and dilatation in 1948.[4] He believed, as did Matthews and Belsey,[10] that increasing anterograde flow across the right ventricular outflow tract not only achieved adequate palliation but was more likely to promote the growth of the pulmonary valve ring, trunk, and arteries.[2] Recently balloon dilatation of the right ventricular outflow tract has been used as a non-surgical method of increasing anterograde pulmonary blood flow[6,7] and has produced adequate palliation. A further report has indicated that an increase in the size of the pulmonary valve ring, trunk, and arteries may also occur after balloon dilatation.[11]

In our patient palliation after balloon dilatation, though initially effective, was limited by further increase in the infundibular obstruction. After another balloon dilatation to facilitate the passage of a large sheath through the infundibulum, we were able to proceed with myocardial resection. Histology confirmed that the resected pieces were myocardium and fibrous tissue.

Atherectomy catheters are currently under evaluation in peripheral vascular and coronary artery disease.[12,13] We showed the successful application of an atherectomy catheter for the resection of the infundibulum in a child with tetralogy of Fallot.

We suggest that transcatheter resection of the infundibulum may be important in the palliation of the tetralogy of Fallot and possibly other conditions characterised by fibromuscular stenosis. However, further modifications of the atherectomy catheter are needed for this technique to become widely accepted.

We thank Dr J B Simpson, cardiologist at Sequoia Hospital, Redwood City, California, USA, and Mr B Hinch of Intervention Ltd, UK

1 Kirklin JW, Barratt-Boyes BG *Cardiac surgery* New York Wiley Medical, 1986:749–802
2 Brock RC. Late results of palliative operations for Fallot's tetralogy. *J Thorac Cardiovasc Surg* 1974,67 511–8.
3 Kirklin JW, Blackstone EH, Kirklin JK, Pacifico AD, Aramendi J, Bargeron LM Surgical results and protocols in the spectrum of tetralogy of Fallot *Ann Surg* 1983,198:251–64.
4 Brock RC Pulmonary valvulotomy for relief of congenital pulmonary stenosis. Report of 3 cases. *Br Med J* 1948,i:1121–6
5 Brock RC, Campbell M. Infundibular resection or dilatation for infundibular stenosis. *Br Heart J* 1950;12:403–24.
6 Qureshi SA, Kirk CR, Lamb RK, Arnold R, Wilkinson JL. Balloon dilatation of the pulmonary valve in the first year of life in patients with tetralogy of Fallot a preliminary study *Br Heart J* 1988;60·232–5.
7 Qureshi SA, Ladusans EJ, Parsons JM, Baker EJ, Tynan MJ. Efficacy of percutaneous balloon dilatation of the pulmonary outflow tract as palliation of tetralogy of Fallot [Abstract] *Br Heart J* 1989,61:482
8 Kirklin JW, Blackstone EH, Pacifico AD, Brown RN, Bargeron LM Jr Routine primary repair vs two stage repair of tetralogy of Fallot. *Circulation* 1979;60 373–86
9 Rittenhouse EA, Mansfield PB, Hall DG, *et al*. Tetralogy of Fallot selective staged management. *J Thorac Cardiovasc Surg* 1985;89.772–9
10 Matthews HR, Belsey RHR. Indications for the Brock operation in current treatment of tetralogy of Fallot. *Thorax* 1973;28:1–8.
11 Parsons JM, Ladusans EJ, Qureshi SA. Growth of the pulmonary artery after neonatal balloon dilatation of the right ventricular outflow tract in an infant with the tetralogy of Fallot and atrioventricular septal defect *Br Heart J* 1989;62·65–8.
12 Simpson JB, Matthew RS, Robertson GC, *et al* Transluminal atherectomy for occlusive peripheral vascular disease *Am J Cardiol* 1988,61 96G–101G
13 Simpson JB, Robertson GC, Selmon MR Percutaneous coronary atherectomy [Abstract] *Circulation* 1988,78 (suppl II):326.

Br Heart J 1990;**64**:166–70

ANGLO-AMERICAN CARDIOLOGY

Samuel A Levine's first world war encounters with Mackenzie and Lewis

Charles F Wooley, John M Stang

Abstract

Samuel Albert Levine was a key figure in modern cardiology in the United States. During the first world war he was one of a select group of United States medical officers assigned to the British Military Heart Hospital where he encountered the "British medical giants"—Clifford Allbutt, William Osler, James Mackenzie, and Thomas Lewis. Levine's diary, written when he was a young medical officer during the first world war, presents crisp character sketches of James Mackenzie and Thomas Lewis. The autobiographical vignettes he wrote later in life were more gracious and polished retrospectives.

The Levine perspectives, separated by a half century, contribute to our understanding of the developing fabric of Anglo-American cardiology.

In October 1917 Lieutenant Samuel A Levine wrote from the British Military Heart Hospital, Colchester, England to his Chief, Dr Henry Christian, at the Peter Bent Brigham Hospital, Boston, Massachusetts, USA:

> We have a group of nice men, most of whom you know; Frank Wilson of St. Louis, Rufus Morrison of the Rockefeller, B. S. Oppenheimer and Marcus Rothschild of the Mt. Sinai, William St. Lawrence of New York, besides two Canadians, Thomas Cotton and Ross Jamieson. Dr. Lewis is down here from Monday to Friday and then returns to London. Sir William Osler is to make ward visits with us for the next two days.

Levine (fig 1) was one of a select group of United States and Canadian medical officers assigned "to the British Heart Hospital, in Hampstead, where I worked from August until October 1917. Then the unit was transferred to Colchester, in Essex, where we occupied the old Sobraon Barracks."

Levine recalled this period and his experience with the "British medical giants",[1] the brothers Regii—Allbutt and Osler,[2] and the subjects of the present article—Mackenzie and Lewis—in a series of autobiographical vignettes written late in life. The senior Levine (fig 2) used his 1917 wartime diary to recall his initial impressions; this provided a fresh glimpse of these men seen through a half century perspective.

Figure 1 Samuel Levine: United States medical officer, first world war, at the British Military Heart Hospital. (From the personal collection of Dr S A Levine.)

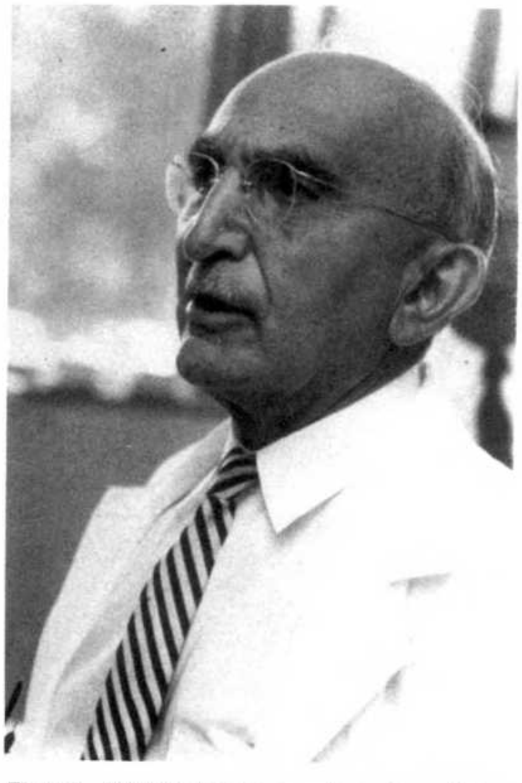

Figure 2 Dr Samuel Levine, consultant: As as visiting professor at The Ohio State University in 1959.

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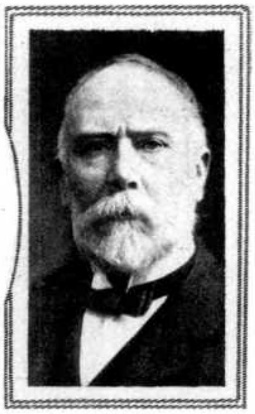

Figure 3 Sir James Mackenzie: From the Illustrated London News 31 January 1925, p 165 (with permission of the Illustrated London News Picture Library).

Levine's first world war diary sketches were crisp, at times brusque, brimming with the certainty and criticism of youth. Conversely, the vignettes written later in life were gracious, polished retrospectives, intended for publication.

James Mackenzie "a tall burly man with all the directness of the North"[3] (figure 3)

When Levine encountered Mackenzie in 1917 he was Sir James Mackenzie, a consultant in London, nearing the end of his active medical practice. He graduated from Edinburgh in 1878; 28 years of practice in industrial Burnley followed. Lewis noted that it was in Burnley that "He (Mackenzie) became by his own impulse and while engaged in the busy routine of a large practice, medical, surgical and obstetrical, an ardent and wholly self-trained investigator of outstanding merit."[4]

The intensity of the man and the extent of his accomplishments during the Burnley experience were best described by Bramwell: "One cannot but marvel at such achievements. The hours for research were literally snatched from the rush of general practice. But in a man of Mackenzie's temperament, the urge to contribute to knowledge and to the welfare of his fellow men is overwhelming and, no matter how extensive his other commitments might be, that urge prevails."[3]

Mackenzie's clinical observations in patients with heart disease and his innate curiosity provided the stimulus for the development of the first world war British Military Heart Hospital.[5] He was supported in this activity by William Osler, Regius Professor of Medicine at Oxford, and Clifford Allbutt, Regius Professor of Medicine at Cambridge. As the war progressed and an ever increasing number of soldiers presented with peculiar disorders of the heart,[6] government policy and health insurance expenditures, the manpower needs of the armed forces, disability determinations, and the economics of pensions became major concerns in the United Kingdom.

When the Heart Hospital came into existence early in 1916 Osler and Allbutt joined Mackenzie as consultants and Thomas Lewis was the medical director.

JAMES MACKENZIE: A CHARACTER SKETCH FROM SAMUEL A LEVINE'S WARTIME DIARY WRITTEN IN THE AUTUMN OF 1917

We then visited Sir James Mackenzie and had a very interesting talk with him for an hour. Several points stood out quite definitely. Sir James, I believe, is growing old and therefore refractory and stubborn in his ideas. He seems to be bitter against Sir William Osler, his book of medicine and his teachings. As Sir James asked what the various men in the States, whom he knew, were doing, he always remarked 'barren soil' or 'that won't lead him anywhere', etc. Other peoples' work did not seem important in the least. He thought that medicine was retrogressing. People were giving up chloroform for ether because they did not use chloroform properly. 'We in Edinburgh never had any difficulty with chloroform'.

Medical research is not conducted properly. A man should have ten years general practice before he enters a research laboratory. One great mistake that Mackenzie makes is that he judges all medicine and medical men, in general, from his own experiences. He has done an epoch making piece of work in the last thirty years while carrying on a general practice. In fact, I think that he stands out as one of the very great men in clinical medicine of the past century. However, similar repetitions are apt to be very rare. In spite of my difference of opinion to his views, it is most interesting to hear such unorthodoxic opinions expressed by such a leading figure.

SIR JAMES MACKENZIE: LEVINE'S RECOLLECTIONS LATER IN LIFE

The third consultant at the British Heart Hospital and one of the giants of the British school of cardiology of that era was Sir James Mackenzie. Dr. Mackenzie was quite different from the other two men (Allbutt, Osler) I've described.[2] He was a Scotsman and was somewhat dour and given to broad philosophic generalization. He frowned on the introduction of instrumentation in the diagnosis of disease despite the fact that he developed the ink polygraph machine (known more familiarly as a lie detector machine). This device recorded certain physiologic responses as represented by mechanical or electrical impulses, such as pulse waves, breathing movements, and blood pressure, and was of great benefit to the medical profession.

His resentment may have been enhanced when such a patient would be sent abroad to "convalesce" at a health spa such as bad Nauheim or Baden-Baden. Probably he was distressed at the idea of English folk spending British pounds in a foreign country. In fact, Mackenzie had something of a "chip on his shoulder" regarding the rich. During one of our more intimate conversations after he had returned from London, he said that he would go to London every so often to earn some good guineas from the rich and spend them on the poor of St. Andrews.

Before leaving the question of the good or harm that might come from using the stethoscope, it must be appreciated that heart disease may be present for many years (especially in patients suffering from valvular disease) before heart failure occurs. Auscultation allows one to detect the murmurs indicative of valvular regurgitation when no symptoms are apparent. Only years later will the history reveal that the heart is beginning to fail. Patients and their physicians should know this information, even if there is no need for digitalis or restriction of activity, because certain measures may be taken or advice given that will prevent or delay future difficulties.

PERSPECTIVE

Mackenzie's biographies were written by R McNair Wilson and Alex Mair. *The Beloved Physician* by Wilson was contemporary, romantic, and written in the heroic mode. Mair's extensive biography was an authorised version, written as he noted, "under the spell."

A more critical biographer might have analysed Mackenzie's paradoxical behaviour. While Levine held him in high regard—"At that time probably the most outstanding cardiologist in the world"—Levine succinctly noted several of the paradoxes. One was Mackenzie's view of technology and instrumentation. Despite his international reputation based on the translation of bedside physiology with the polygraph and the resultant ability to record, define, and analyse arrhythmias, Mackenzie thought technology inappropriate and distracting for the practitioner. Lawrence analysed the origins of this recurrent theme, the distrust of technology, a persisting concern in British medicine in his description of the "new cardiology" in Britain from 1880–1930.[7]

Levine addressed another paradox—Mackenzie's approach to auscultation. Although he was a product of the auscultatory era, his long experience at Burnley stimulated him to emphasise functional capacity and "to overthrow the dictatorship of the stethoscope which dominated cardiology for nearly a hundred years." Mackenzie was motivated by the noble impulse to avoid invalidism in civil life. When Mackenzie's dogma about ignoring apical systolic murmurs was put in practice at the Heart Hospital, however, the result was long term confusion in understanding the frequency and course of mitral valvar regurgitation.

Levine appreciated the clinical wisdom that Mackenzie mined at Burnley through analysis of "the careful records of his patients (which) revealed the significance of symptoms." He recognised Mackenzie's contributions to the understanding of the natural history of certain cardiac conditions, and the emphasis placed on functional capacity ("a heart is what a heart can do"). Many of these attributes found expression in Levine's clinical practice and medical writings.

Thomas Lewis: background

Thomas Lewis (fig 4) burned with a clear blue flame—extraordinary energy and intelligence focused through an incredible intensity. Although Lewis has not as yet had a definitive biographer, there is a great deal of information available about his wartime experience at the Heart Hospital of "soldier's heart". Howell analysed the soldiers heart story in detail—the redefinition of heart disease in soldiers that took place at the Heart Hospital and the contribution of the foundation of the specialty and its technology to the process.[6] Thomas Lewis stood at the centre of these activities, conceiving and directing the beginnings of scientific inquiry into the classification of cardiac disease and the pathogenesis of functional cardiac disorders that took place at Hampstead and at Colchester. Lewis's further evolution as a clinical scientist proceeded along different pathways after the war, in part as a result of these experiences.

Figure 4 Thomas Lewis (right) with Ross Jamieson in 1917 (from the personal collection of Dr S A Levine).

THOMAS LEWIS: A CHARACTER SKETCH FROM SAMUEL A LEVINE'S WARTIME DIARY WRITTEN IN THE AUTUMN OF 1917

Dr. Lewis impresses one as having rare qualities and a perfectly sound intellect. He hardly displays evidence of genius. But like many men of ability, he is apt to be stubborn in his opinions and refractory to other peoples' views. By doing intensive and laborious work of a fundamental nature on the physiology of the heart, he has been able to make quite a distinct contribution to our knowledge. One is immediately impressed by his writings and his conversation as to his clearness of thought and expression. He always seems to have a reasonable explanation for the points he maintains. He is quick in getting at the kernel of a discussion. In general, he is a skeptic of most scientific work and this trait, although generally helpful, frequently leads him astray. A frequent error that men of prominence make is to consider their opinion in other subjects as authoritiative as that in the one which has been their main work. Dr. Lewis, I believe, is apt to make this mistake at times.

His accuracy of statement is supreme. But there are times and things, about which it is just as improper to talk in the most accurate terms as it is to weight out a milligram on a crude balance. It is rather disturbing if one has ever to be cautious about the remarks one makes in his presence. This feeling has not come up in my personal experience but with others it has. One never feels he has come close to Dr. Lewis's inner personality. He does not open out his self very widely. He does not make you admire or love him, but rather respect him and stand in awe before him.

There are very few things about which he does not know a great deal. He has a deep interest in birds and photography, both of which he has combined most appropriately. The art that is mixed up in his soul is of a rare type. It mingles with the artistic a peculiar pragmatic and materialistic strain that is not commonly seen. Above all, he is an extremely keen man.

SIR THOMAS LEWIS: LEVINE'S RECOLLECTIONS LATER IN LIFE

The fourth of the British giants attached to the British Heart Hospital was Thomas Lewis (later Sir Thomas). He was an amazing young man—energetic, frank, brusque, and quick in his manner—and had a most keen intellect. We had been warned that he was "not an easy man to live with." However, this did not appear to be the case regarding us Americans. He took a fancy to us and was always kindly disposed. In fact, he and I became fast friends and remained so throughout his life. Lewis had firm opinions and convictions on many subjects. I was even courageous enough to differ with him, even though I was only a young physician. In fact, we sometimes engaged in rather heated medical discussions, each taking a diametrically opposite view.

He was the only man I knew who remained a civilian throughout the war and yet held a responsible post as chief of a military hospital. He never joined the army and never wore a military uniform. How he was able to do this with the government's consent is not clear. It must have required a good deal of courage, since many a man would have felt uneasy about strangers regarding him as a slacker during those trying war years. He was only about 40 years old at the time. Perhaps he feared that if he joined the regular Royal Army Corps he might be sent to Mesopotamia, Egypt, or some other place where he would be forced to do work that he was not particularly qualified to perform. In his unique way, he succeeded in obtaining just the right post to do his job and to benefit the war cause best.

Lewis always had a happy family working under him at the British Heart Hospital. Most of the medical officers were Americans, although there were a few British, Canadians, and occasionally other colonials. Eventually, they would leave the Sobraon barracks at Colchester and join the American forces in France. This arrangement proved valuable to us Americans and was also of great help in staffing the hospital for the British. The hospital also proved to be a training ground where we Americans learned something about solider's heart, or what was later called neurocirculatory asthenia (NCA).[8]

One incident illustrates Lewis's independence of mind. On this occasion I was sitting beside him at our mess table at luncheon when a messenger brought him a note requesting that he see some military official who had just arrived. We finished our lunch in our customary unhurried fashion and walked out to an adjoining sitting room, where I found Lewis talking to a staff officer. Later I learned that the officer was the Inspector General of the British Medical Corps. It so happened that just before lunch, Lewis had asked Frank Wilson and me if we would like to go out for a bird walk after our meal, and we had eagerly accepted the invitation. Standing beside Lewis and the Inspector General was Captain Thomas Cotton, regarded as second-in-command of the professional staff at our hospital. I overheard Lewis say that he was sorry not to be able to accompany the Inspector General on the tour of inspection but he had a previous appointment and that Captain Cotton would be his guide instead. Had he been in the military, I doubt whether he could have avoided complying with the wishes of the Inspector General just to take a bird walk with two American lieutenants.

During one of our medical discussions, Lewis made a remark that left a strong impression on me. He stated that in most cases, before a research project was begun, he could fairly well predict what would eventually prove to be the essential conclusions of the study. What he meant was that the investigations were planned in order to prove something he already thought to be true.

Another time we had a brisk debate regarding the relative importance of valvular and muscular factors in the progress of chronic rheumatic valvular diseases. He insisted that it did not matter much whether the valve was slightly or markedly deformed; the important determinant was the health and strength of the heart muscle. His reasoning was that on postmortem examinations, valves are at times only slightly distorted and at other times markedly so. I took the opposite view, maintaining that except for the acute stage of active rheumatic carditis, seen particularly in children, the degree of valvular deformity was all important and that the heart muscle played a secondary and comparatively unimportant role. In fact to bring this opinion clearly in focus, I stated that if one could introduce a purse-string suture around the mitral valve to cause significant and progressive constriction of that valve, one could reproduce the clinical features of heart failure seen in cases of mitral stenosis without introducing elements such as infection or a change in the coronary blood flow. In a word, I propounded the view that mechanical narrowing of the valve in itself was of primary significance.

In further discussions, I recall asking whether patients who had rheumatic infections during childhood would develop progressive congestive heart failure many years later from heart muscle disease if there were no valvular defects. If the heart muscle was so important in causing heart failure in chronic rheumatic valvular disease, we ought to see middle-aged people with heart failure with no valvular disease who had rheumatic fever in childhood. Clearly, except during the acute stage of rheumatic carditis (really pancarditis), late chronic heart failure does not occur as a consequence of rheumatic infections when the valves are not involved. The exceptions are when an independent factor such as hypertension or coronary artery disease is present.

Another argument offered was that when the valvular deformity was very slight and the patient died, the cause of death was some other disease or condition, such as bacterial endocarditis, pulmonary or arterial embolism, coronary artery disease, or an infection. In more recent years, since the introduction of modern cardiac valvular surgery, the importance of the valvular element in rheumatic heart disease has been definitely established. Interestingly, Mackenzie's view was similar to that of Lewis.

About six years later, Dr. Elliott C. Cutler and I reported the first case of mitral stenosis in medical history in which the patient, a young girl, underwent operation, improved, and lived for 4½ years. The operation was performed by Dr. Cutler at the Peter Bent Brigham Hospital on May 20, 1923. I sent a reprint of our article to Mackenzie, and in his reply he indicated no enthusiasm for the possible value of surgery and, in fact, hinted that not much was to be expected from correcting the valve defect, since the main trouble was muscular rather than valvular. This remained the predominant view among British cardiologists for many years thereafter.

PERSPECTIVE

Dr Levine's vignette of Lewis is the most personal of his recollections of the "four British giants". Levine obviously enjoyed his contact with Lewis, the intellectual stimulation, and was impressed by Lewis's sense of independence. The entire Heart Hospital experience left deep impressions on the young Levine.

The vignette of Lewis also allows us a view of the young Sam Levine with the juices flowing, engaging one of the best minds of the era, enjoying the contest, and delighting in the debates, discussions, and controversy.

Levine also reflected on the next leap forward, the Cutler-Levine 1923 cardiotomy and valvotomy for mitral stenosis. This was, as Allbutt said, "a bold enterprise," but one for which both Mackenzie and Lewis had little enthusiasm.

The participation of Thomas Lewis,[9] James Mackenzie,[10] Clifford Allbutt,[11] and William Osler[12] in the Heart Hospital experience was a focal point in modern cardiology, and a junction between the "old" and "new" cardiology in Great Britain.[7] Later in the war the Heart Hospital served as "a training ground," a contact point between the more senior British cardiologists and their young United States and Canadian counterparts.

Samuel A Levine's recollections of the interactions among the first world war British and the United States medical officers give us a glimpse of events that became cornerstones for future relations between British and American cardiology for the rest of the century.

Anglo-American cardiology

Anglo-American cardiology had its origins during this era. William Osler brought Canadian, United States, and British medical experiences and ties to the establishment of the British Military Heart Hospital. Allbutt travelled and lectured in the United States and Canada and delivered the invited Lane lectures on the cardiovascular system in San Francisco in 1898. Mackenzie also travelled extensively in the United States as a tourist in 1885 when he was a general practitioner; he was an international figure when he returned to North America in 1918 as a member of a British wartime delegation. Mackenzie and Allbutt brought the wisdom of decades of medical practice and reputations as consultants and authorities in early cardiovascular medicine to the development of the Military Heart Hospital.

Lewis visited the United States in 1914, gave the Herter lectures in Baltimore, the Harvey lecture in New York City, and was a visiting professor at the Peter Bent Brigham Hospital in Boston. Burchell traced the extraordinary impact Lewis had on American cardiology.[13]

Krikler spoke of Anglo-American links that resulted when Alfred E Cohn worked with Thomas Lewis in 1909, returned to the United States, "brought the first string galvanometer to the Western Hemisphere," and joined the staff of the Rockefeller Institute for Medical Research in 1911.[14] Francis Fraser, a University of Edinburgh graduate, travelled in the other direction; he worked with Cohn as a British research fellow at the Rockefeller and later returned and served with Lewis at the Heart Hospital in Hampstead. Paul Dudley White and Jonathan Meakins were in Lewis's laboratory just before the war. Samuel Levine worked with Cohn at the Rockefeller before his British Military Heart Hospital experience with Lewis.

Lewis's laboratory at the University College Hospital, London, and the Heart Hospital at Hampstead and later at Colchester were centres for Anglo-American exchange during the first two decades of the 20th century. Samuel Levine, Frank Wilson, Bernard Oppenheimer, Marcus Rothschild, Paul Dudley White, Thomas Cotton, Ross Jamieson, Jonathan Meakins, Hubert Starling, John Parkinson, Francis Fraser, Rufus Morrison, William St Lawrence—met, interacted with, or were influenced by each other and their contacts with the "four British giants". All these experiences were part of the developing fabric of Anglo-American cardiology: old physicians and young; contacts, impressions, strong imprints; teachers and mentors; shared experiences, associations, collaborations, friendships; bright young minds encountering the legends of their time. These are the roots of the United States and Canadian cardiology that may be recognised 80 years later.

Mrs Samuel A Levine and Dr Herbert Levine allowed us to review, select, and edit material from Dr Samuel Levine's first world war diary and from his autobiographical vignettes written later in life for inclusion in this article.

We thank the following for financial support: Overstreet Cardiovascular Teaching and Research Laboratory, Division of Cardiology, The Ohio State University College of Medicine, and The Columbus Foundation, Columbus, Ohio.

1 Wooley CF, Stang JM. Samuel A Levine and his World War I experience *Am J Cardiol* 1988;62:952–6.
2 Wooley CF, Stang JM. Samuel A Levine and his World War I encounters with the brothers Regii, Allbutt and Osler. *Am J Cardiol* 1990,65:669–73.
3 Bramwell C. John Hay and the founders of the Cardiac Club *Br Heart J* 1965;27·849–55
4 Lewis T. Sir James Mackenzie, M.D., L.L.D., F R C.P., F.R S *Heart* 1925–26;12:1–7.
5 Wooley CF. From irritable heart to mitral valve prolapse: World War I, the British experience and James Mackenzie. *Am J Cardiol* 1986;57·463–6.
6 Howell JD "Soldier's heart". the redefinition of heart disease and speciality formation in early twentieth-century Great Britain. *Med Hist [Suppl]*:1985;5:34–52.
7 Lawrence C. Moderns and ancients: The "new cardiology" in Britain 1880–1930. *Med Hist [Suppl]* 1985;5·1–33.
8 Wooley CF. From irritable heart to mitral valve prolapse: World War I—the US experience and the origin of neurocirculatory asthenia. *Am J Cardiol* 1987;59:1183–6.
9 Wooley CF. From irritable heart to mitral valve prolapse. World War I, the British experience and Thomas Lewis *Am J Cardiol* 1986,58:844–9
10 Wooley CF From irritable heart to mitral valve prolapse: World War I, the British experience and James Mackenzie *Am J Cardiol* 1986,57 463–6.
11 Wooley CF. From irritable heart to mitral valve prolapse: World War I, the British experience and Clifford Allbutt. *Am J Cardiol* 1987;59.353–7.
12 Wooley CF. From irritable heart to mitral valve prolapse. the Osler connection. *Am J Cardiol* 1984;53:870–4.
13 Burchell H. Sir Thomas Lewis: his impact on American cardiology *Br Heart J* 1981;46 1–4.
14 Krikler DM. Wolff-Parkinson-White syndrome: long follow-up and an Anglo-American historical note. *J Am Coll Cardiol* 1983,6:1216–8.

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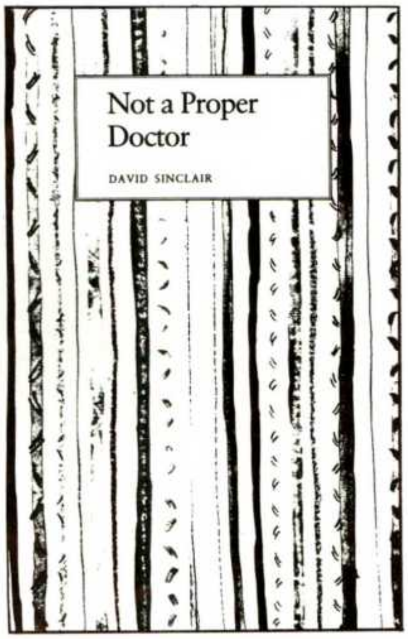

When is a medical practititoner "not a proper doctor"? According to the author (or rather his wife) when he is a professor of anatomy. David Sinclair was intent on a career in surgery when he graduated from St Andrew's University but fate, mainly in the shape of the second world war, decreed otherwise. He eventually became the first professor of anatomy at the University of Western Australia by way of the RAMC, Porton Down, researching the effects of mustard gas in Queensland, and the department of human anatomy at Oxford. His peregrinations did not, however, stop there; he returned to this country to take up the regius chair of anatomy at Aberdeen University and before retirement became director of postgraduate medical education at Perth, Western Australia.

Professor Sinclair looks back at his varied life—at the forces, people, and choices that have shaped it. There are moments of joy, moments of sadness and regret, throughout a central core of humour and compassion—the stuff that "proper" doctors are made of.

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R. Rettig, D. Ganten, University of Heidelberg; **F. C. Luft**, Indiana University (Eds.)

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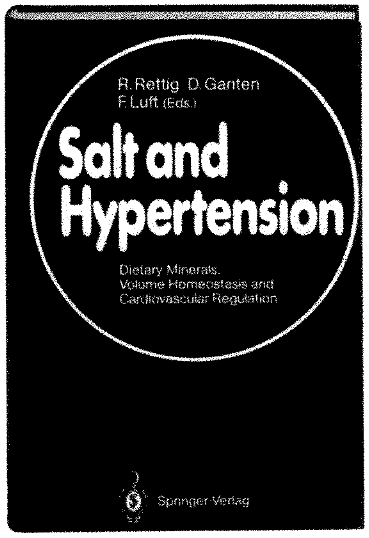

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D. Ganten, University of Heidelberg;
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E. M. Vaughan Williams, Oxford University (Ed.)

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Coeditor: T. J. Campbell

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Hardcover DM 480,– ISBN 3-540-19239-5

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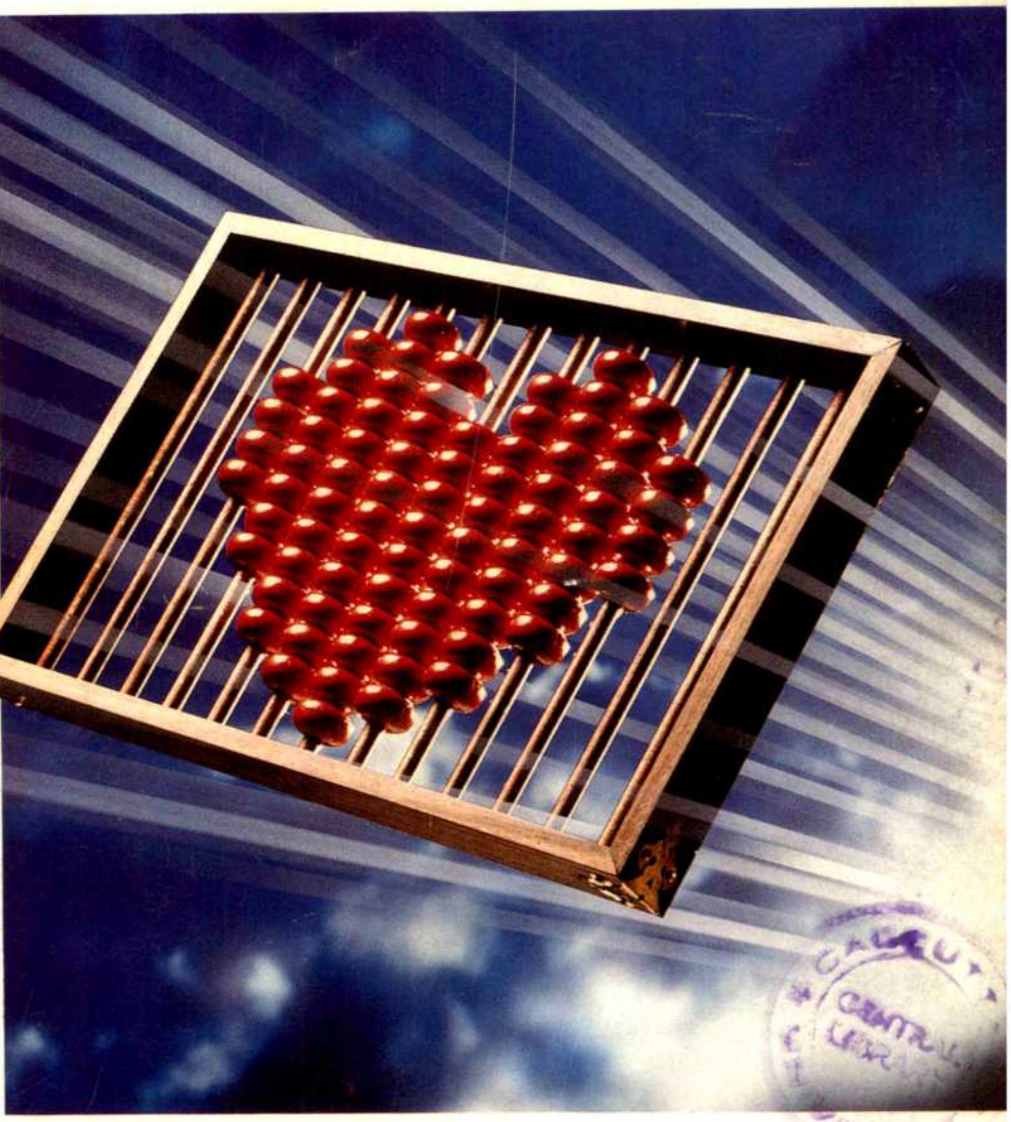

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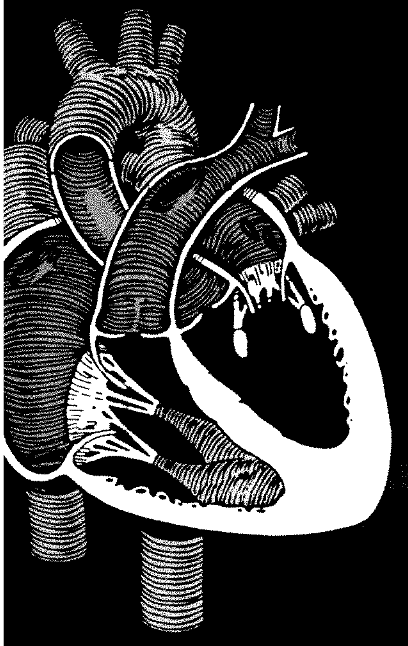

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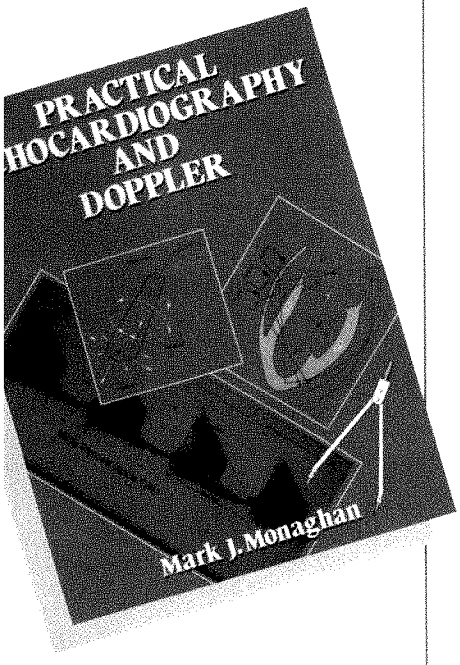

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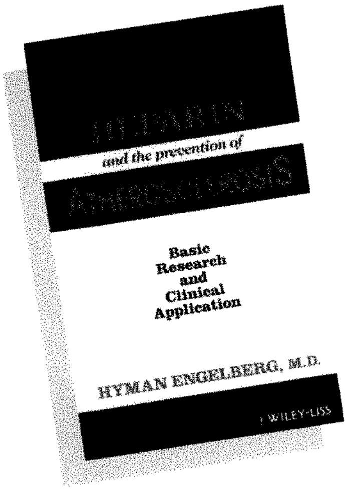
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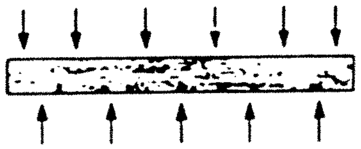

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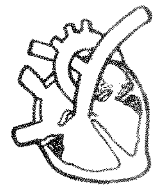

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ERENCES

tudy Group, *Europ. Heart J.*, 1987, **8**, 77.

ipid Research Clinics Programme, *J. Amer. med. Ass.*, 1984, **251**, 351-364.

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BRITISH
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Editorial

Endocavitary ablation of atrioventricular conduction

Endocavitary electrical ablation of atrioventricular conduction can be used to treat the symptoms of supraventricular tachycardia by creating complete heart block and allowing the ventricular rate to be controlled by an implanted pacemaker. Since it was first described in 1982[1] the technique has become an established alternative to surgical ablation in patients with supraventricular tachycardia that is refractory to medical treatment.[2]

Conventional method of ablation

For conventional ablation 200–300 J shocks are delivered via an endocardial wire that is positioned to record an optimal His bundle deflection. Patients selected for ablation usually have atrial flutter or fibrillation,[3] but atrioventricular nodal re-entry tachycardia and atrioventricular re-entry tachycardia through an accessory atrioventricular connection may also be treated.

The technique is largely successful, creating complete heart block in 60–80% of patients,[3] and beneficially modifying conduction in a further 10–30%. Complete failure is reported in around 10%. There are several disadvantages to conventional ablation that deserve attention: a general anaesthetic is required; a degree of uncontrolled myocardial damage is produced by the explosive discharge, as shown by the subsequent rise in cardiac enzymes[4]; there are acute and chronic complications, some of which may be severe[3 5]; a permanent pacemaker must be implanted after a successful procedure[3]; pacemaker function may be disrupted if a repeat ablation session is necessary[5]; and there is evidence of diffuse damage to left ventricular function in long term studies of exercise tolerance after ablation.[6 7]

Other ablation sites

When the same conventional technique was applied to other myocardial sites it was generally less successful and potentially more hazardous.[3 5 8 9] The success rate for the ablation of accessory pathways[10 11] was much lower than that reported for ablation of atrioventricular conduction, with the exception of Warin's group in Bordeaux whose innovative catheterisation techniques allowed them to overcome many of the deficiencies of the conventional technique.[12] Nevertheless, ablation of accessory pathways must be regarded as experimental.[13]

Ablation of ventricular tachycardia was often accompanied by complications[3 14–17] and procedure-related mortality was high. The World Registry reported that the cure rate was 18% without drugs, with a further 41% of patients responding to drugs that had been ineffective before ablation; the procedure-related mortality was 8%.[3] Some groups have claimed greater success rates,[15 18] but because of the high risk the technique must be regarded as experimental.

Direct ablation for atrial arrhythmias[19 20] has also been attempted with conventional techniques. If successful, these direct ablations would provide a complete cure without the creation of a complete heart block.

In general, the conventional method is not sufficiently safe for widespread use to be recommended for other than ablation of atrioventricular conduction. Many regard conventional ablation as a relatively safe technique in this setting, and newly developed methods of ablation are always applied initially to the atrioventricular junction because it is the safest site. So ablation of atrioventricular conduction is a clinical procedure and also a testing ground for new methods that may later be more applicable to ventricular tachycardia or accessory pathways.

Aims of ablation

Creation of complete heart block, and subsequent pacemaker dependence, is a drastic solution to supraventricular tachycardia with a rapid ventricular response. A medical treatment that created a complete block would not be used, and it is not surprising that attempts have been made recently[21–23] to modify rather than destroy atrioventricular conduction so that the ventricular rate could be controlled without the need for a pacemaker. But how long do the immediate effects of ablation last? If ablation initially increases the PR interval from 0·1 to 0·3 seconds, what will be its long term value, and indeed will there be any measurable long term effect on atrioventricular conduction? This highlights the difficulties in predicting the relation between the shock intensity and the extent of the acute lesion produced, and in predicting the eventual size of the lesion. The basic mechanisms by which lesions are created during ablation procedures, despite extensive investigation,[24 25] remain controversial. There is, however, no doubt that conventional ablation with high energy DC shocks has greater effects in the short term than in the long term.[26] The central area of damage is surrounded by considerable oedema and if the target structure is within this oedematous region, an apparently successful ablation may prove to be a failure hours or days later when the oedema resolves. In addition, other, more complex phenomena that are little understood can result in the late appearance[27] or disappearance of heart block. In our own series, one patient mysteriously resumed atrioventricular conduction after nine months in complete heart block.[28]

Problems and pitfalls

The major drawback of using high energy shocks and conventional electrodes is the highly explosive nature of the discharge.[29] A vapour globe that can be up to 4 cm in diameter is formed and can rupture the coronary sinus or damage the underlying myocardium.

To improve the safety of the procedure, several modifications have been proposed. Active fixation of permanent pacing electrodes[30] reduced the energy required for ablation to four shocks of 50 J. More recently the energy requirements have been further reduced by use of non-arcing DC ablation, which uses a modified power source[31] and electrode[32]; the energy required for ablation with this system is around 20 J. This method was effective for ablation of the atrioventricular node[28] and also for treatment of ventricular tachycardia[33 34] and ablation of accessory pathways. Although the safety margin is improved by use of lower energy shocks, the patient still needed general anaesthetic. A multicentre international trial is underway to assess the technique for ablation of atrioventricular conduction.

The use of radiofrequency energy through standard or suction electrode catheters has also achieved much attention.[35] This variation allows most ablations to be performed without general anaesthesia, but more importantly a graduated effect may be achieved through short applications of radiofrequency energy and observation of the prolongation of the PR interval. Radiofrequency ablation has the disadvantage of being extremely focal: a thermal lesion is more localised than an electrical lesion and therefore positioning of the electrode catheter must be precise. Furthermore, if the electrode at the tip of the wire exceeds 100°C it will char the tissue and produce a thermal barrier that prevents further effective ablation. Research into the better control of tip temperature[36 37] may improve the results of radiofrequency ablation or modification, which are currently only moderately successful. However, because a general anaesthetic is not needed the technique can be repeated with less harm to the patient than other methods of ablation. In addition, doubts remain about the applicability of the technique to ablation of ventricular tachycardia because the size of the lesion that radiofrequency can produce is limited. Presentations[38-41] at the 1990 Scientific Sessions of the American College of Cardiology seemed to indicate a better success rate with the low energy DC technique than with radiofrequency ablation when the object was to produce a complete atrioventricular block.

Other techniques of interest are transcatheter lasers[42] (problems of perforation have prevented clinical application so far), thermal loop ablation (again entirely experimental), and transcoronary alcohol ablation; this latter technique uses selective coronary catheterisation and infusion of ethanol to create a limited myocardial lesion. It has previously been used as the last resort in cases of untreatable ventricular tachycardia,[43] but very recent work in the United Kingdom suggests that better control of lesion size may make the technique feasible for ablation of atrioventricular conduction.[44]

Conclusions

The mechanism responsible for the damage created during ablation procedures—whether with high energy DC, low energy DC, or radiofrequency electrical current—is not sufficiently well understood to permit the design of an optimal system. Also our understanding of the mechanics of conduction through the atrioventricular node is still sufficiently vague to hinder our attempts at its modification by endocavitary methods.

What is apparent is the need for further research into safer and more reliable methods of ablation if the technique is to make the major leap forward that coronary angioplasty has made—to be used as an alternative to drug treatment rather than as a last resort. If this goal is to be reached, we must be able to reliably modify chronic atrioventricular conduction with negligible risk to the patient and without the need to implant a permanent pacemaker and we must also be able to treat the patient with ventricular tachycardia or an accessory pathway with at least moderate success, but, above all, without risk.

The physical specifications of the lesions required for ablation or modification of different arrhythmias will vary; and so too will the optimal technique. Once this is taken into account, and the desire to prove that one system is better than all the others *in all situations* is suppressed, ablation research can begin to focus on providing clinicians with a set of tools with which they may reliably tackle a wide range of clinical tachycardias.

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1 Scheinman MM, Morady F, Hess DS, Gonzalez R. Transvenous catheter technique for induction of damage to the atrioventricular junction in man [Abstract] *Am J Cardiol* 1982,49:1013
2 Scheinman MM Catheter techniques for ablation of supraventricular tachycardia *N Engl J Med* 1989,320 460–1
3 Evans GT Jr, Scheinman MM, Zipes DP, *et al* The Percutaneous Cardiac Mapping and Ablation Registry final summary of results *PACE* 1988,11·1621–6
4 Baraka M, Fontaine G, Deveaux N, Abdelali S, Frank R, Grosgogeat Y. Activite enzymatique de la creatine kinase et de son isoenzyme MB dans la fulguration endocavitaire *Ann Cardiol Angeiol (Paris)* 1987,36 335–40.
5 Fisher JD, Kim SG, Matos JA, *et al.* Complications of catheter ablation of tachyarrhythmias occurrence, protection and prevention *Clin Prog Electrophysiol Pacing* 1985,3 292–8
6 Schofield PM, Bowes RJ, Brooks N, Bennett DH. Exercise capacity and spontaneous heart rhythm after transvenous fulgaration of atrioventricular conduction *Br Heart J* 1986,56.358–65.
7 Trappe HJ, Klein H, Frank G, Lichtlen P Erfahrungen mit VVI-, QT-Zeit- und aktivitatsgesteuertein Schrittmachersystemen bei Patienten mit transvenoser, elektrischer Ablation der atrioventrikularen Uberleitung *Z Kardiol* 1986,75·737–43
8 Sebag C, Lavergne T, Millat B, *et al* Rupture of the stomach and the esophagus after attempted transcatheter ablation of an accessory pathway by direct current shock *Am J Cardiol* 1989,63 890–1.
9 Bardy GH, Ivey TD, Coltorti F, Stewart RB, Johnson G, Greene HL Developments, complications and limitations of catheter-mediated electrical ablation of posterior accessory atrioventricular pathways. *Am J Cardiol* 1988,61 309–16
10 Morady F, Scheinman MM, Kou WH, *et al* Long-term results of catheter ablation of a posteroseptal accessory atrioventricular connection in 48 patients *Circulation* 1989,79 1160–70
11 Ward DE, Rowland E, Wainwright RJ, Camm AJ. Electrical ablation of junctional tachycardias showing a long RP interval. *Eur Heart J* 1989; 10 718–24
12 Warin JF, Haissaguerre M Fulguration of accessory pathways in any location. report of seventy cases *PACE* 1989;12 215–8.
13 Buxton AE Catheter ablation of atrioventricular bypass tracts Still an investigational procedure *Circulation* 1989,79:1388–90.
14 Morady F, Scheinman MM, Griffin JC, Herre JM, Kou WH Results of catheter ablation of ventricular tachycardia using direct current shocks. *PACE* 1989,12:252–7
15 Borggrefe M, Breithardt G, Podczeck A, Rohner D, Budde T, Martinez-Rubio A Catheter ablation of ventricular tachycardia using defibrillator pulses electrophysiological findings and long-term results *Eur Heart J* 1989,10 591–601
16 Montserrat P, Haissaguerre M, Le Metayer P, Warin JF,. Blanchot P. Complications immediates de la fulguration des tachycardias ventriculaires et voies accessoires. Analyse de 318 chocs endocavitaires. *Ann Cardiol Angeiol (Paris)* 1989;38 191–6
17 Haissaguerre M, Warin JF, Lemetayer P, Guillem JP, Blanchot P. Fulguration of ventricular tachycardia using high cumulative energy results in thirty-one patients with a mean follow-up of twenty-seven months *PACE* 1989,12 245–51.
18 Fontaine G, Tonet JL, Frank R, Rougier I. Clinical experience with fulguration and antiarrhythmic therapy for the treatment of ventricular tachycardia Long-term follow-up of 43 patients. *Chest* 1989;95:785–97.
19 Chauvin M, Brechenmacher C A clinical study of the application of endocardial fulguration in the treatment of recurrent atrial flutter *PACE* 1989,12·219–24
20 Gillette PC, Wampler DG, Garson A, *et al.* Treatment of atrial automatic tachycardia by ablation procedures *J Am Coll Cardiol* 1985;6:405–9.
21 Huang SK, Bharati S, Graham AR, Gorman G, Lev M. Chronic incomplete atrioventricular block induced by radiofrequency catheter ablation *Circulation* 1989,80 951–61.
22 Epstein LM, Scheinman MM, Langberg JJ, Chilson D, Goldberg HR, Griffin JC. Percutaneous catheter modification of the atrioventricular node A potential cure for atrioventricular nodal reentrant tachycardia. *Circulation* 1989,80 757–68
23 Kappenberger L, Goy JJ, Fromer M Modulation of atrioventricular conduction in patients with supraventricular tachycardias. *New Trends in Arrhythmias* 1990,6:589–94
24 Bardy GH, Coltorti F, Ivey TD, Stewart R, Green HL. Effects of high energy electrical shocks delivered to the atrium of the coronary sinus. In: Scheinman MM, ed. *Catheter ablation of cardiac arrhythmias.* Norwell, MA Martinus Nijhoff, 1988 67–96
25 Fontaine G. The effects of high-energy DC shocks delivered to ventricular myocardium. In. Scheinman MM, ed. *Catheter ablation of cardiac arrhythmias.* Norwell, MA Martinus Nijhoff, 1988 97–114.
26 Bardy GH, Emery M, Ivey TD, Greene HL, Reichenbach DD. The relative importance of voltage vs charge on tissue injury during catheter mediated

27 Bru P, Levy S, Metge M, Comte R, Lacombe P, Gerard R. Remote occurrence of high degree heart block following failure of transcatheter AV junctional ablation: incidence and clinical significance. *PACE* 1987;10:937–42.

28 Rowland E, Cunningham D, Ahsan A, Rickards A. Transvenous ablation of atrioventricular conduction with a low energy power source. *Br Heart J* 1989;62:361–6.

29 Bardy GH, Coltorti F, Ivey TD, *et al.* Some factors affecting bubble formation with catheter-mediated defibrillator impulses. *Circulation* 1986;73:525–38.

30 Holt PM, Boyd EG, Crick JC, Sowton E. Low energies and Helifix electrodes in the successful ablation of atrioventricular conduction. *PACE* 1985;8:639–45.

31 Cunningham D, Rowland E, Rickards AF. A new low energy power source for catheter ablation. *PACE* 1986;9:1384–90.

32 Ahsan AJ, Cunningham D, Rowland E, Rickards AF. Catheter ablation without fulguration: design and performance of a new system. *PACE* 1989;12:131–5

33 Rowland E, Cunningham D, Ahsan AJ, Rickards AF. Low energy ablation of ventricular tachycardia using a modified power source and a modified electrode [Abstract]. *Eur Heart J* 1988,9(suppl 1):261

34 Jordaens L, Roelandt R, Palmer A, Van Wassenhove E, Clement D. Ablation of ventricular tachycardia of right ventricular origin with low energy shocks. *PACE* 1989;12:911–6

35 Huang SK, Bharati S, Graham AR, Lev M, Marcus FI, Odell RC. Closed chest catheter desiccation of the atrioventricular junction using radiofrequency energy—a new method of catheter ablation. *J Am Coll Cardiol* 1987,9:349–58

36 Haverkamp W, Hindricks G, Gulker H, *et al.* Coagulation of ventricular myocardium using radiofrequency alternating current: bio-physical aspects and experimental findings. *PACE* 1989;12:187–95

37 Wittkampf FH, Hauer RN, Robles de Medina EO. Control of radiofrequency lesion size by power regulation. *Circulation* 1989;80: 962–8.

38 Schamp DJ, Langberg JJ, Chin MC, *et al.* Comparison of catheter ablation of atrioventricular junction using radiofrequency energy and direct current shock [Abstract]. *J Am Coll Cardiol* 1990,15:19A.

39 Huang SKS, Chenarides JG, Cuenoud H, Gasdia G, Bazgan ID. Long term follow up of radiofrequency cathether ablation of the atrioventricular node for supraventricular tachyarrhythmias [Abstract]. *J Am Coll Cardiol* 1990;15:19A.

40 Lemery R, Talajic M, Roy D, Girard A, Montpetit M. Low energy direct current ablation in patients with supraventricular tachycardia [Abstract]. *J Am Coll Cardiol* 1990,15:20A

41 Ahsan AJ, Rowland E, Cunningham D, Rickards AF. Low energy ablation of atrioventricular conduction: efficacy maintained, energy and barotrauma reduced, safety improved [Abstract]. *J Am Coll Cardiol* 1990;15,133A

42 Narula OS. Laser catheter technique for induction of AV nodal delays: possible applications for management of supraventricular tachyarrhythmias. In: Scheinman M, Fontaine G, eds. *Ablation in cardiac arrhythmias.* Mount Kisco, NY: Futura, 1987:405–17.

43 Brugada P, de Swart H, Smeets JL, Wellens HJ. Transcoronary chemical ablation of ventricular tachycardia. *Circulation* 1989;79:475–82

44 Sneddon JF, Ward DE, Simpson IA, Linker NJ, Camm AJ. Transcoronary alcohol ablation of the atrioventricular node [Abstract]. *Br Heart J* 1990,64:100–1

Br Heart J 1990,64:234-5

Editorial

Mitral valve surgery: to repair or replace?

Heart valve prostheses remain imperfect substitutes for the native valve. There are problems of tissue failure in bioprostheses[1 2] and the drawbacks of long term anticoagulation, predominantly with mechanical prostheses.[3] There is a growing awareness that the native mitral valve annulus and chordae tendineae are essential components of normal ventricular morphology and function,[4 5] and improved understanding of the pathological anatomy of mitral valve disease has encouraged the development of operations designed to repair the valve's structural components, singly or in combination.[6] Improvements in non-invasive echocardiography and Doppler ultrasound techniques allow more accurate preoperative assessment of diseased valves[7] while refinements in techniques for myocardial preservation give more intraoperative time for precise evaluation and reconstruction. There is growing evidence that mitral valve repair improves short and long term survival and is associated with fewer thromboembolic complications than valve replacement.[8-16]

The simplest conservative procedure, closed mitral valvotomy, was reported in 1925[17] and remains an important operation though it is not generally regarded as a "repair" procedure. The earliest reports of mitral valve repair procedures, suture annuloplasty under direct vision and on cardiopulmonary bypass, were in 1957.[18 19] Initial enthusiasm for this procedure was dispelled, however, by reports of high operative mortality and loss of clinical improvement in up to 50% of patients within three years.[20 21]

Valve replacement because of its more predictable results became the recommended procedure for mitral insufficiency.[22] In the early 1970s several groups, most notably Carpentier and colleagues, reported that, compared with replacement, mitral valve repair improved survival and functional state and reduced thromboembolic complications.[8 9] Recently, more support for repair rather than replacement has been generated by David and colleagues.[23 24] They reported a postoperative increase in left ventricular end diastolic pressures and decreased ejection fractions when the chordae were disrupted in patients undergoing valve replacement, compared with repair or replacement when these structures were preserved.[23 24] Others, however, dispute these findings.[14]

Mitral valve reconstruction ranges from at its simplest, commissurotomy, through annuloplasty, to complex repair procedures, in which the chordae tendineae are refashioned and transplanted.[6 25 26] With surgical repair good results depend on the precise evaluation of the underlying morphology of the mitral valve—its leaflets, annulus, commissures, chordae tendineae, and papillary muscles.[6] Carpentier *et al* produced a classification of leaflet abnormalities and emphasised the need to tailor the repair procedure to the exact pathological process; they attributed previous poor repair results to a failure to do this.[8] Complex repair procedures have not been widely applied because they may be technically more difficult, demand greater subjective assessment, require increased intraoperative time, and have a longer learning curve and less predictable results than replacement (at least in the learning period).[27] Intraoperative assessment of the efficacy of repair procedures is difficult and not entirely satisfactory. It has, until recently, relied on methods such as visual inspection for leakage after filling the ventricle, either during ventricular arrest or with an active beating heart. The increasing availability of transoesophageal or surface echocardiography at the time of surgery should, however, allow improved intraoperative assessment of the repair procedure and should reduce the likelihood of an unsatisfactory result.[28]

Which valves are suitable for reconstruction? There are no absolute rules but, generally, regurgitant valves are more suitable than stenotic valves for reconstructive procedures. One exception is the purely stenotic valve with non-calcified and pliable leaflets, predominantly seen in younger patients in developing countries. In such countries closed valvotomy is the usual treatment because cost precludes open valvotomies, which require extracorporeal circulation. The cost of radiographic facilities and catheters also controls the use of percutaneous balloon dilatation of such valves in developing countries.

Few surgeons would disagree that the end stage rheumatic mitral valve (typified by retracted, fibrotic and/or calcified leaflets, and a fused subvalvar apparatus) requires replacement. In contrast, regurgitant mitral valves characterised by non-calcified floppy leaflets, annular dilatation, and elongated chordae are more amenable to repair—as are those with chordal rupture, which is frequently associated with floppy valves but may be idiopathic. Demographic changes and the decline in the incidence of rheumatic heart disease have increased the numbers of patients with floppy mitral valves that may be suitable for repair procedures. Indeed, pure mitral valve incompetence is now most commonly due to the floppy mitral valve syndrome (mitral valve prolapse), but such incompetence can also be congenital, idiopathic, ischaemic, infective, or cardiomyopathic.[29-31]

Duran suggested that up to 40% of all mitral valves are suitable for reconstruction[25] and Carpentier estimated that 5% of aortic valves, 50% of rheumatic mitral valves, and 90% of floppy mitral valves are suitable for repair.[27] Floppy mitral valve disease was the reason for 40% of the mitral valve surgery performed in 1141 patients at the Cleveland Clinic between 1985 and 1988 and was usually suitable for operative correction.[26] The procedures needed for surgical repair include ring annuloplasty, chordal shortening, resection and transposition of a normal leaflet to fill defects created by resection of flail leaflets, and occasionally transposition of the papillary muscle head.[25 26]

Several groups reported better short and long term survival and functional state accompanied by a reduction in thromboembolic and anticoagulant-related complications, endocarditis, and the need for reoperation after mitral valve repair compared with replacement.[8-16] Unfortunately, substantial differences in preoperative characteristics in the repair and replacement groups, which could themselves influence outcome, make it difficult to draw conclusions from these studies.[8-16] The possibility that improved survival in patients undergoing repair procedures may simply reflect selection of a population with less advanced disease is supported in a recent paper by Galloway and colleagues.[16] This group compared operative and late results in patients with porcine valve replacements (975), mechanical valve replacements (169), and Carpentier type mitral valve reconstructions (280). Although operative and five year mortality were reduced in the repair group, multivariate analysis showed this to be an effect of younger age and better preoperative myocardial function rather than type of operation.

In view of the patient numbers and the expense and length of follow up that would be required, comparison of mitral valve reconstruction and replacement in a prospective randomised trial is unlikely; indeed it is questionable whether such a trial would be ethical or practical. It is as inappropriate to attempt to repair an end stage, calcified, retracted mitral valve with a densely fused subvalvar apparatus as to replace a stenotic valve with fused, non-calcified, pliable leaflets with a prosthetic valve. The increasing prevalence of degenerative valve disease and growing dissatisfaction with currently available prostheses is likely to result in an increasing number of repair procedures despite their being more technically demanding and requiring greater experience. It is likely, but as yet unproven, that reconstructive surgery of the mitral valve in appropriately selected patients will give better long term results and fewer complications than prosthesis insertion.

Improvements in non-invasive preoperative assessment of diseased valves allow a high degree of accuracy in predicting those in whom reconstructive procedures are likely to be successful. For rheumatic mitral disease repair is virtually always feasible (and highly desirable) for pure stenosis without significant calcification; and may be achieved by closed valvotomy, particularly if sinus rhythm is still present. Where regurgitation is a consequence of annular dilatation or the floppy valve syndrome, repair is also likely to be successful (as it is in rheumatic regurgitation if seen at an early stage). In contrast, the thickened, retracted, immobile, and calcified leaflets commonly seen in end stage rheumatic mitral valve disease in most Western countries are rarely suitable for repair.

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1 Starr A, Grunkemeier GL The expected lifetime of porcine valves *Ann Thorac Surg* 1989,48 317–8
2 Teoh KH, Ivanov J, Weisel RD, Darcel IC, Rakowski H Survival and bioprosthetic valve failure Ten-year follow-up *Circulation* 1989, 80(suppl 1) 8–15
3 Edmunds LH Jr Thrombotic and bleeding complications of prosthetic heart valves *Ann Thorac Surg* 1987;44.430–45
4 Spence PA, Peniston CM, David TE. *et al.* Toward a better understanding of the etiology of left ventricular dysfunction after mitral valve replacement an experimental study with possible clinical implications. *Ann Thorac Surg* 1986,41 363–71
5 Hansen DE, Cahill PD, DeCampli WM, *et al* Valvular ventricular interaction importance of the mitral apparatus in canine left ventricular systolic performance. *Circulation* 1986,73.1310–20
6 Carpentier A Mitral valve reconstructive surgery. In: Jamieson SW, Shumway E, eds *Rob and Smith's operative surgery* 4th ed London Butterworths, 1986.405–14
7 Bloomfield P, O'Boyle JE, Parisi AF Non-invasive investigations for the diagnosis of mitral valve disease In Ionescu MI, Cohn LH, eds *Mitral valve disease diagnosis and treatment* London Butterworths, 1985 53–86
8 Carpentier A, Deloche A, Dauptain J, *et al* A new reconstructive operation for correction of mitral and tricuspid insufficiency *J Thorac Cardiovasc Surg* 1971,61 1–13
9 Kerth WJ, Sharma G, Hill JD, Gerbode F A comparison of the late results of replacement and of reconstructive procedures for acquired mitral valve disease *J Thorac Cardiovasc Surg* 1971,61 14–22
10 Carpentier A, Chauvaud S, Fabiani JN, *et al* Reconstructive surgery of mitral valve incompetence ten-year appraisal *J Thorac Cardiovasc Surg* 1980;79 338–48
11 Yacoub M, Halim M, Radley-Smith R, McKay R, Nijveld A, Towers M Surgical treatment of mitral regurgitation caused by floppy valves repair versus replacement *Circulation* 1981,64(suppl II) 210–6
12 Abedo OA, Ross JK Surgical treatment of ruptured mitral valve chordae A comparison between valve replacement and valve repair *Thorac Cardiovasc Surg* 1984,32 139–42
13 Perier P, Deloche A, Chauvaud S, *et al* Comparative evaluation of mitral valve repair and replacement with Starr, Bjork, and porcine valve prostheses *Circulation* 1984 70(suppl 1) 187–92
14 Angell WW, Oury JH, Shah P A comparison of replacement and reconstruction in patients with mitral regurgitation *J Thorac Cardiovasc Surg* 1987,93 665–74
15 Sand ME, Naftel DC, Blackstone EH, Kirklin JW, Karp RB A comparison of repair and replacement for mitral valve incompetence *J Thorac Cardiovasc Surg* 1987,94 208–19
16 Galloway AC, Colvin SB, Baumann FG, *et al* A comparison of mitral valve reconstruction with mitral valve replacement intermediate-term results. *Ann Thorac Surg* 1989,47 655–62.
17 Souttar HS The surgical treatment of mitral stenosis *Br Med J* 1925;ii 603–6
18 Lillehei CW, Gott VL, DeWall RA, Varco RL Surgical correction of pure mitral insufficiency by annuloplasty under direct vision *Journal-Lancet (Minneapolis)* 1957,77.446–9
19 Merendino KA, Bruce RA One hundred and seventeen surgically treated cases of valvular rheumatic heart disease with preliminary report of two cases of mitral regurgitation treated under direct vision with aid of a pump oxygenator *JAMA* 1957,164 749–55
20 Bigelow WG, Kuypers PJ, Heimbecker RO, Gunton RW. Clinical assessment of the efficiency and durability of direct vision annuloplasty *Ann Surg* 1961,154 320–9
21 Ellis FH Jr, Callahan JA, McGoon DC, Kirklin JW Results of open operation for acquired mitral valve disease *N Engl J Med* 1965,272 869–74
22 Effler DB, Favaloro R, Groves LK Heart valve replacement *Ann Thorac Surg* 1965,1 4–24
23 David TE, Uden TE, Strauss HD The importance of the mitral valve apparatus in left ventricular function after correction of mitral regurgitation. *Circulation* 1983,68(suppl 2) 76–82
24 David TE, Burns RJ, Bacchus CM, Druck MN Mitral valve replacement for mitral regurgitation with and without preservation of chordae tendineae *J Thorac Cardiovasc Surg* 1984,88 718–25
25 Duran CG Conservative surgery of the mitral valve—ring annuloplasties In· Ionescu MI, Cohn LH, eds *Mitral valve disease Diagnosis and treatment* London. Butterworths, 1985 179–90
26 Cosgrove DM Mitral valve repair in patients with elongated chordae tendineae *Journal of Cardiac Surgery* 1989,3 247–52
27 Carpentier A Cardiac valve surgery the "French correction" *J Thorac Cardiovasc Surg* 1983,86:323–37
28 Kyo S, Takamoto S, Matsumura M, *et al* Immediate and early postoperative evaluation of results of cardiac surgery by transeosophageal two-dimensional Doppler echocardiography *Circulation* 1987,76(suppl V) V113–21
29 McKay R, Yacoub MH Clinical and pathological findings in patients with "floppy" valves treated surgically *Circulation* 1973,48(suppl III) 63–73
30 Hanson TP, Edwards BS, Edwards JE. Pathology of surgically excised mitral valves one hundred consecutive cases *Arch Pathol Lab Med* 1985,109 823–8
31 Olson LJ, Subramanian R, Ackermann DM, Orszulak TA, Edwards WD Surgical pathology of the mitral valve a study of 712 cases spanning 21 years *Mayo Clin Proc* 1987,62 22–34

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ORIGINAL ARTICLES

Systemic pattern of free radical generation during coronary bypass surgery

S W Davies, S M Underwood, D G Wickens, R O Feneck, T L Dormandy, R K Walesby

Abstract

Diffuse impairment of ventricular function after cardiac surgery may be related to the generation during reperfusion of the myocardium of free radicals derived from oxygen. Fifteen patients undergoing elective coronary bypass surgery were studied by previously described assays for peroxidised lipids and for isomerised lipids which were used as indices of free radical activity. Serial blood samples were obtained from systemic arterial, mixed venous, and coronary sinus catheters before, during, and after the ischaemic period. The patients underwent coronary artery surgery on cardiopulmonary bypass with a membrane oxygenator, relative hypothermia 30–34°C, and intermittent cross-clamping of the aorta. During the ischaemic periods there were no significant changes in the indices of free radical activity. During the reperfusion phase there was a significant increase in free radical indices in arterial and mixed venous blood. A small rise in free radical indices in coronary venous blood was not statistically significant.

These data indicate that free radical activity is increased in patients shortly after the cessation of cardiopulmonary bypass. The pattern of distribution between the different sampling sites suggests that much of the observed increase in isomerised and peroxidised lipids originates from tissues other than the myocardium.

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During coronary artery surgery the heart undergoes periods of ischaemia with either cardioplegia or aortic cross-clamping and induced ventricular fibrillation. There is sometimes a significant global deterioration in left ventricular function that is attributed to this ischaemia and to the subsequent reperfusion.[1 2] Reperfusion is though to generate free radicals derived from oxygen when oxygen is reintroduced during reperfusion of the myocardium.[3–5] Free radicals are chemical species with an unpaired electron and are highly reactive. Free radicals derived from oxygen can damage a wide variety of biological molecules including proteins, lipids, and nucleic acids.[6] This will impair cell structure and function; in particular, damage to membrane lipids may allow the influx of ionised calcium.[6–8] It has been suggested that changes in the cell membrane are also responsible for reperfusion arrhythmias.[9]

Diffuse pulmonary impairment can also occur after bypass surgery; this is similar both histologically and functionally to the adult respiratory distress syndrome associated with severe systemic infection or major trauma.[10] During cardiopulmonary bypass neutrophils were sequestered in the lungs,[11 12] with the release of enzymes and the generation of lipids damaged by free radicals.[11 13 14]

Both the diffuse impairment of ventricular function and the pulmonary impairment after bypass surgery may therefore be related to the generation of free radicals derived from oxygen. To investigate this we used two independent measures of free radical damage to study patients during bypass surgery.

Patients and methods

PATIENT SELECTION

Fifteen patients undergoing elective coronary artery bypass grafting gave informed consent for the placement of coronary sinus and pulmonary arterial catheters and for blood sampling during the bypass procedure. All were men (aged 41 to 67 years (mean age 54)). Patients had good left ventricular function as judged by the preoperative angiogram (left ventricular ejection fraction >55%) and had no evidence of pulmonary disease as judged by chest *x* ray, lung volumes, and carbon monoxide gas transfer (diffusing capacity).

PROCEDURE

After premedication a Baim-Rothman catheter was inserted into the coronary sinus and its position confirmed (*a*) by obtaining blood samples with oxygen saturation <45% and (*b*) by radiography during the injection of small volumes of non-ionic contrast medium. A Swan-Ganz catheter was inserted into the central pulmonary artery and a radial artery cannula was inserted.

Anaesthesia was induced with a benzodiazepine/narcotic/relaxant sequence and the patient was ventilated with 50% oxygen in nitrogen. Anaesthesia was maintained with further intravenous or inhalational anaesthetics, as required. Patients were perfused during cardiopulmonary bypass with non-pulsatile flow from a sheet membrane oxygenator (COBE membrane lung) with a 2 litre crystalloid prime. The surgical technique con-

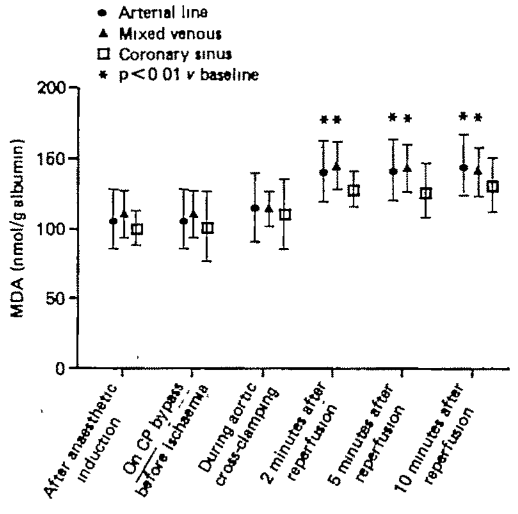

Figure 1 Plasma concentrations (mean (SEM)) of malondialdehyde during cardiopulmonary bypass, measured as thiobarbituric acid reacting material.

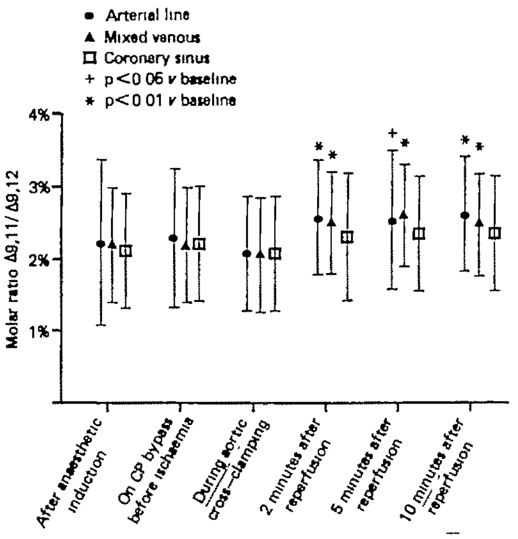

Figure 3 Molar ratios (mean (SEM)) of 18:2(9,11)/18:2(9,12) in plasma phospholipids during cardiopulmonary bypass

sisted of sequential myocardial revascularisation by vein and internal mammary artery grafts with intermittent cross-clamping of the aorta, ventricular fibrillation, and mild hypothermia 32–34°C.

Serial sets of blood samples were drawn from the mixed venous site (central pulmonary artery during bypass from the venous line to the pump), systemic arterial site (radial artery cannula), and coronary sinus (Baim-Rothman catheter). Blood was drawn into heparinised plastic syringes, and the plasma was separated by centrifugation and stored in plastic tubes at −20°C. Samples were taken (*a*) after induction of anaesthesia; (*b*) after systemic heparinisation, on cardiopulmonary bypass; (*c*) during the last of the periods of cardiac ischaemia (aortic cross-clamping with fibrillation); and 2,5, and 10 minutes after coronary reperfusion.

LIPID PEROXIDATION ASSAY

Material that reacted with thiobarbituric acid was measured according to a modification of the fluorimetric method of Yagi.[15 16] This is preferred to the spectrophotometric assay, in which bilirubin, glucose, and sialic acid may interfere. Volumes in the procedure differed from Yagi's original method in two respects: plasma samples of 50 μl rather than 20 μl were used, and adduct was extracted into 3 ml butan-1-ol rather than 5 ml. This increases the sensitivity and improves the repeatability of the assay. To take into account haemodilution during bypass the plasma albumin was determined on a Beckman Astra 8 with a bromocresol green reagent, and results were expressed as grams thiobarbituric acid reactive material per gram albumin.

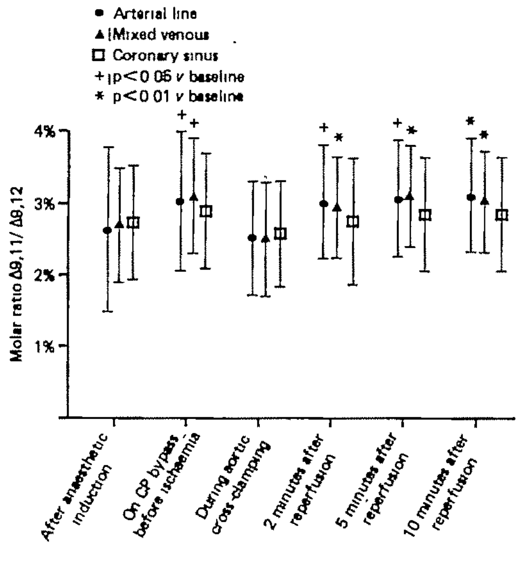

Figure 2 Molar ratios (mean (SEM)) of 18:2(9,11)/18:2(9,12) in plasma free fatty acids during cardiopulmonary bypass.

LIPID ISOMERISATION ASSAY

In vitro experiments showed that free radicals can cause isomerisation of polyunsaturated fatty acyl chains withut causing their oxidation.[17] The isomerisation most studied has been the conversion of linoleic acid (18:2(9,12)) to octadeca-9,11-dienoic acid (18:2(9,11)), which accounts for over 90% of diene conjugation in human plasma, tissues, and tissue fluids.[18] A high performance liquid chromatographic method can measure both the isomer 18:2(9,11) and the parent 18:2(9,12) in plasma.[19] Plasma samples were separated into free fatty acid and phospholipid fractions, and these were analysed separately. To take into account haemodilution during bypass, the concentration of 18:2(9,11) was expressed as the molar ratio of isomerised product to parent molecule—that is, 18:2(9,11) × 100%/18:2(9,12).

STATISTICAL ANALYSIS

Baseline values of the indices of free radical activity varied widely and because a normal distribution could not be assumed we used non-parametric methods. We used the Wilcoxon matched pairs rank test to make comparisons between different points in time. We adjusted significance values for multiple comparisons using the Bonferroni correction.

Results

The anaesthetic, bypass, and surgical procedures were uncomplicated in all patients and between 1 and 4 grafts were performed in each patient. All patients had an uncomplicated postoperative course without clinical signs of impaired ventricular function with normal echocardiographic appearances and no new changes in the 12 lead electrocardiogram.

Initial values of all the free radical indices varied widely. Concentrations of material reacting with thiobarbituric acid ranged from 66 to 145 ng per gram of albumin. The molar ratio 18:2(9,11)/18:2(9,12) in the phospholipid fraction ranged from 1·45% to 7·57% and the molar ratio in the free fatty acid fraction ranged from 1 92% to 10·36%.

During the period of cardiac ischaemia there were no significant changes in either concentrations of material reacting with thiobarbituric acid or in the molar ratio at any of the sites of sampling. During the reperfusion phase, however, there were several significant changes. The concentration of material reacting with thiobarbituric acid increased significantly in arterial blood ($p < 0\,01$) and in mixed venous blood ($p < 0{\cdot}01$) but increases in coronary sinus blood were smaller and not significant (fig 1). The molar ratio 18:2(9,11)/18:2(9,12) in the free fatty acid fraction increased slightly after systemic heparinisation and the start of cardiopulmonary bypass (fig 2). At the time of reperfusion this molar ratio increased significantly in mixed venous blood ($p < 0{\cdot}01$) and in arterial blood ($p < 0{\cdot}05$); a small increase in the coronary sinus blood was not significant (fig 2). The molar ratio in the phospholipid fraction increased significantly in mixed venous ($p < 0{\cdot}01$) and in arterial blood ($p < 0{\cdot}05$), but again there were no significant changes in coronary sinus blood (fig 3).

Discussion

Protection of the myocardium so as to minimise the impairment of left ventricular function is a major concern during cardiac surgery. Left ventricular function is an independent determinant of prognosis in various cardiac conditions.[20-22] It has been postulated that reperfusion injury makes a significant contribution to postoperative ventricular dysfunction[23]; this is of considerable practical importance in influencing strategies to improve myocardial preservation.

The central role of free radicals derived from oxygen in diverse forms of cardiac disease is increasingly appreciated.[24 25] They have been implicated in anthracycline cardiotoxicity,[26 27] the cardiomyopathy of thalassaemia and haemachromatosis,[28 29] and in selenium deficiency cardiomyopathy.[30 31] Most work, however, relates to the phenomenon of reperfusion injury and the implications for cardiac surgery, thrombolysis, and angioplasty.[4 5] Because the free radicals themselves are highly reactive, with life spans of the order of microseconds or shorter, they can only be measured directly in tissues and in cell-free systems by electron spin resonance spectroscopy (electron paramagnetic resonance). The direct detection of free radicals in cardiac cells and tissues has so far been possible only in vitro and in animal experiments.[32 33]

In most studies, free radical activity has been inferred indirectly by measurement of biological molecules that have been damaged so as to produce unusual products. There are assays for damaged proteins and peptides,[34] damaged nucleic acids,[35] and damaged lipids.[36] Lipid damage has been studied in particular detail, and it is known that oxygen free radicals can initiate a self-propagating chain reaction of lipid peroxidation[37]; thus in published studies, the most commonly used indices of free radical activity have been based on lipid peroxidation. Best known is the assay of malondialdehyde that uses the reagent thiobarbituric acid; there are, however, some limitations in the use of this assay. Although material reactive to thiobarbituric acid is mainly derived from cyclic endoperoxides of lipids that are the result of free radical damage, it is not entirely specific for these.[38 39] Furthermore, some common biological substances may interfere with the spectrophotometric measurement of such material.[40]

Also not all free radical damage to lipids results in peroxidation, and so will not be detected by an assay for malondialdehyde. In vitro experiments showed that free radicals can cause isomerisation of polyunsaturated fatty acyl chains, without causing their oxidation.[17] It therefore seems that there are two possible pathways of lipid damage after free radical interaction (fig 4) and thus an index of each pathway is necessary to assess fully the extent of lipid damage. The lipid isomerisation most studied has been the conversion of linoleic acid (18:2(9,12)) to octadeca-9,11-dienoic acid (18:2(9,11)),[18 36] and this formed the basis of one of the assays of free radical activity in the present study.

Despite the problems of these indirect measurements they have been widely used in in vitro models and in animal experiments, and suggest considerable generation of free radicals at the time of reperfusion, synchronous with a further decline in myocardial contractile function. Only recently have such measurements been attempted in humans—after surgical revascularisation of the myocardium and during angina induced by pacing.[41-43]

It is possible that the generation of free radicals derived from oxygen is an epiphenomenon and not related to reperfusion damage. In several experimental models, however, there are parallel changes in the degree of cell damage and the level of free radical generation, suggesting a causative role. If perfusion is restored to the ischaemic zone gradually rather than suddenly, both the level of free radical generation and the extent of structural and functional damage are much reduced.[44] Similarly if perfusion is restored with oxygen-free fluid equilibrated with 100% nitrogen, and oxygen is then gradually reintroduced, there is a similar limitation both of free radical generation and of damage.[45]

Various drugs are thought to protect against damage by free radicals derived from oxygen, either by limiting their generation or by "scavenging" them. These include enzymes (superoxide dismutase, catalase), molecules with thiol groups (glutathione, captopril), mannitol, and chelators of transition metal ions

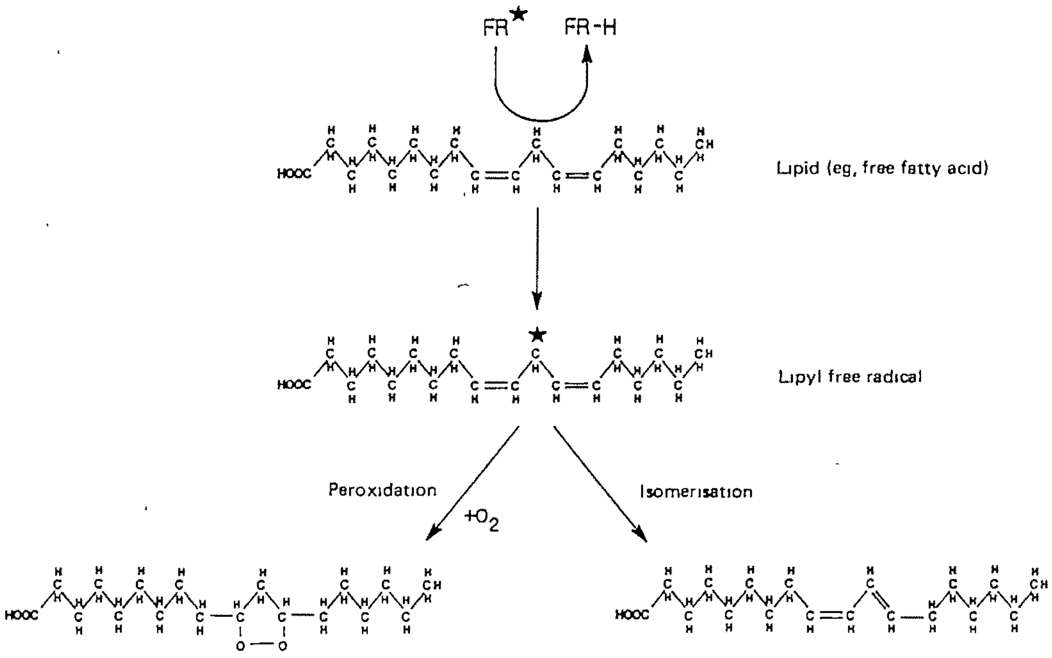

Figure 4 Postulated pathways of lipid damage by free radicals.

(desferrioxamine). In systems in vitro and in animal experiments these drugs both limit the generation of free radicals, as judged by electron spin resonance spectroscopy and by lipid markers, and reduce structural damage, impairment of contraction, and arrhythmias on reperfusion of ischaemic myocardium.[32,46–48] The single common feature of these chemically diverse drugs is that they reduce the impact of free radicals derived from oxygen, and thus the above observations strongly suggest that free radicals play a causal role in reperfusion injury. There has been particular interest in the possible benefits of adding these agents to cardioplegic solutions, but despite the large body of experimental evidence, drugs for scavenging free radicals have yet to be evaluated in clinical practice.

Finally the administration of chemical systems that generate free radicals has been shown to be injurious, both in vitro and in animal models.[32] The generation of free radicals in situ by photochemical reaction also causes severe functional and structural changes resembling reperfusion injury.[49,50] Clearly the corresponding experiments in humans are impossible.

Permanent global impairment of left ventricular function is an important though fortunately uncommon complication of coronary artery surgery with cardiopulmonary bypass.[1,2] It has been suggested that the permanent damage arises at the time of reperfusion, as opposed to the temporary depression of function observed during the period of ischaemia itself.[3,4] A series of ventricular biopsy specimens taken from six patients undergoing operative correction of tetralogy of Fallot showed diene conjugation, a marker of free radical activity, coinciding with myocyte necrosis.[51] In the present study, however, we found no evidence of increased free radical activity in samples of coronary sinus blood at the time of reperfusion. Indeed, there were no significant changes in either of the indices of free radical damage to lipids in coronary sinus blood, during either the ischaemic period of fibrillation and cross-clamping, or at 2, 5, and 10 minutes after coronary reperfusion. In contrast, there were significant increases in these indices in the systemic blood samples; this suggests that much of the observed rise originated from tissues other than the myocardium.

Similar increases in the molar ratio in free fatty acid in venous blood were seen in normal individuals after the administration of 5 000 units heparin,[52] and the increased molar ratio in free fatty acid in the present study may simply reflect heparinisation. Heparin did not cause changes in the molar ratio in phospholipid,[52] and thus cannot account for the increase after bypass. The increase in material reactive to thiobarbituric acid was proportionally greater than the increases in the molar ratio and in the absolute concentration of 18:2(9,11). The isomer 18:2(9,11) is not a peroxidation product and might be expected to increase under anoxic, ischaemic conditions rather than on reperfusion and reoxygenation.

None of the 15 patients in the present study suffered any measurable impairment of left ventricular function, so we do not know whether or not severe perioperative left ventricular impairment would have been associated with an increase in free radical markers in the coronary sinus blood. Certainly in these patients with uncomplicated procedures the increase in free radical markers was *least* in the coronary sinus samples, and did not represent a significant change from the baseline value.

The site of origin of these lipids damaged by free radicals is not defined by the present study, but other work suggests that the lungs are a major source. At the time of restoration of the circulation and of perfusion to the heart, perfusion to the lungs is also restored and there is evidence of white cell sequestration within the lungs.[11,12] Activated components of the complement system, markers of white cell degranulation, and markers of free radical activity were all detectable in the pulmonary effluent blood at this time.[11,13,14] Though few studies have attempted directly to link these changes with functional or structural impairment, they may well underly the diffuse pulmonary impairment that is common after bypass and which sometimes causes the clinically important syndrome resembling adult respiratory distress syndrome.[10]

CONCLUSIONS

The increase in both peroxidised and isomerised lipids in the systemic circulation during the first few minutes of reperfusion was consistent with free radical damage at this time. This rise was least in blood from the coronary sinus, suggesting that much of the rise originated from tissues other than the myocardium. Slightly different patterns of change in lipids damaged by free radicals were seen, depending on which index of free radical damage was used.

We recommend that further studies should (*a*) specifically sample the coronary sinus as well as systemic sites; (*b*) use more than one index of free radical activity to assess reliably the total extent of lipid damage via the different pathways. The methods and problems of the assays of free radical markers have been fully described by others.[18 40] Because other factors may interfere with the assays diet and drug treatment must be monitored.

1 Hultgren HN, Miyagawa M, Buck W, Angell WW. Ischemic myocardial injury during cardiopulmonary bypass surgery. *Am Heart J* 1973;85 167–76
2 Roberts WC, Bulkley BH, Morrow AG Pathologic anatomy of cardiac valve replacement a study of 224 necropsy patients. *Prog Cardiovasc Dis* 1973,15 539–87
3 Jennings RB, Reimer KA. Factors involved in salvaging ischemic myocardium–effect of reperfusion of arterial blood. *Circulation* 1983,68(suppl I) I 25–36.
4 Braunwald E, Kloner RA Myocardial reperfusion. a double-edged sword *J Clin Invest* 1985;76 1713–9.
5 McCord JM Oxygen-derived free radicals in postischemic tissue injury *N Engl J Med* 1985,312 159–63.
6 Hess ML, Manson NH. Molecular oxygen: friend or foe? The role of the oxygen free radical system in the calcium paradox, oxygen paradox and ischemia/reperfusion injury. *J Mol Cell Cardiol* 1984,16.969–85.
7 Hammond B, Hess ML. The oxygen-free radical system potential mediator of myocardial injury *J Am Coll Cardiol* 1985;6 215–20
8 Elz JS, Panagiotopoulos S, Nayler WG Reperfusion-induced calcium gain after ischemia *Am J Cardiol* 1989, 63(suppl E) 7E–13E
9 Manning AS, Coltart DJ, Hearse DJ Ischaemia and reperfusion-induced arrhythmias in the rat. Effects of xanthine oxidase inhibition with allopurinol *Circ Res* 1984,55. 545–8.
10 Ratliffe NB, Young WA, Hackel DB, Mikat E, Wilson JW. Pulmonary injury secondary to extra-corporeal circulation. *J Thorac Cardiovasc Surg* 1973;65·425–32.
11 Westaby S Neutrophil protease enzymes and oxygen free radicals as mediators of pulmonary membrane damage. *Prog Clin Biol Res* 1987,236A 75–86
12 Martin RR Alterations in leukocyte structure and function. In· Hwang NHC, Gross DR, Patel DJ, eds. *Quantitative cardiovascular studies clinical and research applications of engineering principles* Baltimore. University Park Press, 1979.419–54.
13 Hammerschmidt DE, Stroncek DF, Bowers TK, *et al.* Complement activation and neutropenia occurring during cardiopulmonary bypass. *J Thorac Cardiovasc Surg* 1981;81·370–7
14 Kirklin JK, Westaby S, Blackstone EH, Kirklin JW, Chenoweth DE, Pacifico AD Complement and damaging effects of cardiopulmonary bypass *J Thorac Cardiovasc Surg* 1983,86:845–57.
15 Yagi K A simple fluorimetric assay for lipoperoxide in blood plasma *Biochem Med* 1976,15:212–6
16 Yagi K. Assay for serum lipid peroxide level and its clinical significance In: Yaki K, ed *Lipid peroxides in biology and medicine* New York Academic Press, 1982 223–41.
17 Chipault JR, Privett OS, Mizuno GR, Nickell EC, Lundberg WO. Effect of ionising radiations on fatty acid esters. *Ind Eng Chem* 1957,49:1713–20
18 Cawood P, Iversen SA, Dormandy TL. The nature of diene conjugation in biological fluids. In. Bors W, Saran M, Tait D, eds. *Oxygen radicals in chemistry and biology*. Berlin Walter de Gruyter, 1984.355–8.
19 Iversen SA, Cawood P, Dormandy TL. A method for the measurement of a diene-conjugated derivative of linoleic acid, 18.2(9,11), in serum phospholipid, and possible origins *Ann Clin Biochem* 1985,22:137–40.
20 Borer JS, Rosing DR, Miller RH, *et al* Natural history of left ventricular function during 1 year after acute myocardial infarction comparison with clinical, electrocardiographic and biochemical determinations. *Am J Cardiol* 1980,46:1–12
21 Borow K, Green LH, Mann T, *et al* End-systolic volume as a predictor of postoperative left ventricular performance in volume overload from valvular regurgitation. *Am J Med* 1980,68 655–63
22 Fuster V, Gersh BJ, Guiliani ER, *et al* The natural history of dilated cardiomyopathy *Am J Cardiol* 1981;47 525–31
23 Nayler WG, Elz JS Reperfusion injury laboratory artifact or clinical dilemma? *Circulation* 1986,74 215–21
24 Burrell CJ, Blake DR Reactive oxygen metabolites and the human myocardium. *Br Heart J* 1989,61·4–8.
25 Davies SW. Free radicals and myocardial disease—studies in patients In: Rice-Evans C, ed *Free radicals, diseased states, and anti-radical interventions* London. Richelieu Press, 1989.97–115.
26 Bachur NR, Gordon SL, Gee MV. Anthracycline antibiotic augmentation of microsomal electron transport and free radical formation *Mol Pharmacol* 1977;13.901–10
27 Doroshow JH Effect of anthracycline antibiotics on free radical formation in rat heart. *Cancer Res* 1983,43 460–72
28 Thomas CE, Morehouse LA, Aust SD. Ferritin and superoxide-dependent lipid peroxidation *J Biol Chem* 1985,260 3275–80.
29 Halliwell B, Gutteridge JMC The importance of free radicals and catalytic metal irons in human diseases. *Mol Aspects Med* 1985,8 89–193
30 Johnson RA, Baker SS, Fallon JT, *et al* An occidental case of cardiomyopathy and selenium deficiency *N Engl J Med* 1981,304 1210–2
31 Diplock AT Selenium and free radical defences In Rice-Evans C, ed *Free radicals, diseased states, and anti-radical interventions* London. Richelieu Press, 1989 119–42.
32 Hess ML, Okabe E, Kontos HA. Proton and free oxygen radical interaction with the calcium transport system of cardiac sarcoplasmic reticulum *J Mol Cell Cardiol* 1981,13 767–72.
33 Garlick PB, Davies MJ, Hearse DJ, Slater TF. Direct detection of free radicals in the reperfused rat heart using electron spin resonance spectroscopy *Circ Res* 1987; 61.757–60
34 Henricksen T, Melo TB, Saxebol G. Free radical formation in proteins and protection from radiation damage. In Pryor WA, ed. *Free radicals in biology, vol 2*. New York: Academic Press, 1976 213–56.
35 Henriksen T, Bergenne R, Heiberg H, Sagstuen E. Radical reactions in nucleic acids crystal systems In· Pryor WA, ed. *Free radicals in biology, vol 2*. New York Academic Press, 1976 257–94
36 Lunec J, Dormandy TL Fluorescent lipid peroxidation products in synovial fluid *Clin Sci* 1979,56 53–9
37 Fridovich I. Superoxide radical an endogenous toxicant. *Annu Rev Pharmacol Toxicol* 1983;23 239–57.
38 Muus P, Bonta IL, Den Oudsten SA Plasma levels of malondialdehyde, a product of cyclo-oxygenase dependent and independent lipid peroxidation in rheumatoid arthritis a correlation with disease activity *Prostaglandins Med* 1979,2:63–5.
39 Gutteridge JMC Free radical damage to lipids, amino acids, carbohydrates and nucleic acids determined by thiobarbituric acid reactivity. *Int J Biochem* 1982;14 649–53.
40 Satoh K. Serum lipid peroxide in cerebrovascular disorders determined by a new colorimetric method *Clin Chim Acta* 1978;90:37–43
41 Oldroyd KG, Chopra M, Belch JJF, Cobbe SM Free radical general during pacing induced myocardial ischaemia [Abstract]. *Br Heart J* 1988;59 605–6
42 Meerson FZ, Adikaliev NA, Golubea LY. Prevention of hypoxic heart injury by an anti-oxidant of the hydroxypyridine class [Russian article with English abstract] *Biull Eksp Biol Med* 1981,91 1167–9
43 Ferreira R, Llesuy S, Mieli J, *et al* Assessment of myocardial oxidative stress in patients after myocardial revascularisation. *Am Heart J* 1988;115.307–12.
44 Okamoto F, Allen BS, Buckberg JD, Bugyi H, Leaf J Reperfusion conditions: importance of ensuring gentle versus sudden reperfusion during relief of coronary obstruction. *J Thorac Cardiovasc Surg* 1986,92:613–20.
45 Korthuis RJ, Smith JK, Carden DL Hypoxic reperfusion attenuates postischemic microvascular injury. *Am J Physiol* 1989,256.H315–9.
46 Guarnieri C, Ferrari R, Visioli O, Caldarera CM, Nayler WG. Effect of alpha-tocopherol on hypoxic-perfused and reoxygenated rabbit heart muscle. *J Mol Cell Cardiol* 1978;10 893–906.
47 Forman MB, Puett DW, Cates CU, *et al* Glutathione redox pathway and reperfusion injury. Effect of N-acetyl cysteine on infarct size and ventricular function. *Circulation* 1988,78:202–13
48 Westlin W, Mallain K Does captopril attenuate reperfusion-induced myocardial dysfunction by scavenging free radicals? *Circulation* 1988;77 (suppl I) I 30–9.
49 Hearse DJ, Tosaki A Free radicals and calcium· simultaneous interacting triggers as determinants of vulnerability to reperfusion-arrhythmias in the rat heart. *J Mol Cell Cardiol* 1988;20.213–223.
50 Kusama Y, Bernier M, Hearse DJ. Singlet oxygen-induced arrhythmias· light-response characteristics for photosensitisation by rose bengal [Abstract 1830]. *Circulation* 1988; 78 (suppl II)·II–459.
51 Del Nido PJ, Mickle DAG, Wilson GJ, *et al*. Evidence of myocardial free radical injury during elective repair of tetralogy of Fallot. *Circulation* 1987,76 (suppl II):174–9.
52 Wickens DG, Griffin JR, Maher ER, *et al*. The effect of systemic heparinisation and haemodialysis on plasma octadeca-9,11-dienoic acid (9,11-LA'). *Free Rad Res Comms* 1987,3:99–106.

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**ct licence numbers and
NHS cost:** 'Zestril' 2.5mg
208) 28 tablets, £7.84, 5mg
204) 28 tablets, £9.83, 10mg
205) 28 tablets, £12.13, 20mg
206) 28 tablets, £20.96.
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quest.

I'm sitting on top of the world!

Everyone has a certain zest for life. 'Zestril' lets your hypertensive patients enjoy their's. 'Zestril' is an effective ACE inhibitor from ICI. 'Zestril' is taken once daily, so encouraging good patient compliance.

A valuable aspect of 'Zestril' therapy is that it is well tolerated, and suitable for a wide range of hypertensive patients (for whom conventional therapy is ineffective or inappropriate). Your hypertensive patients will appreciate the convenient dosage and good tolerability of 'Zestril'. It's a therapy they'll find easy to live with – one which helps retain their zest for life. Helps retain that 'sitting on top of the world' feeling.

Zestril
lisinopril ICI

Once daily antihypertensive therapy which helps retain that ***zest for life.***

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H1002 Jan 90

▼ ABBREVIATED PRESCRIBING INFORMATION

PRESENTATION: Tablets containing 10mg and 20mg pravastatin. **INDICATIONS AND ADULT DOSAGE**: Primary hypercholesterolaemia intolerant or not responsive to other forms of therapy, with cholesterol level in excess of 7.8 mmol/litre. Start with 10 mg at night. The usual dosage range is 10-40mg at night. A response is usually seen within 1-2 weeks, with the maximum response from a given dose occurring within 4 weeks. A standard cholesterol lowering diet should be continued. **CONCOMITANT THERAPY**: LIPOSTAT is effective alone or in combination with bile acid sequestrants. **IMPAIRED RENAL FUNCTION AND ELDERLY PATIENTS**: Modification of dose is not normally necessary. **CHILDREN**: LIPOSTAT has not been evaluated in children.

CONTRA-INDICATIONS AND WARNINGS: Hypersensitivity to LIPOSTAT. Active liver disease or unexplained persistent elevations in liver function tests. Pregnancy and breast feeding. Women of child bearing potential unless protected by adequate contraception.

PRECAUTIONS: LIPOSTAT has not been evaluated in patients with homozygous familial hypercholesterolaemia. **LIVER FUNCTION**: Liver function tests should be performed periodically; discontinue if elevated liver enzymes greater than 3 times the upper limit of normal persist. Caution should be exercised in patients with a history of liver disease or alcoholism. Increases in CPK and liver enzymes have occasionally been observed. Use with caution in patients taking cyclosporin, fibric acid derivatives and nicotinic acid.

DRUG INTERACTIONS: No clinically significant effects were seen in a range of studies. **SIDE EFFECTS**: LIPOSTAT is generally well tolerated. Adverse events are usually mild and transient. Side effects include rash, myalgia, headache, diarrhoea, fatigue, nausea/vomiting, non-cardiac chest pain. **OVERDOSAGE**: Treat symptomatically.

PRODUCT LICENCE NUMBERS: LIPOSTAT Tablets 10mg 0034/0286. LIPOSTAT Tablets 20mg 0034/0287. **BASIC NHS PRICE**: 10mg tablets, £16.18 for 28-tablet calendar pack. 20mg tablets, £31.09 for 28-tablet calendar pack. **LEGAL CATEGORY**: POM. LIPOSTAT is a Squibb Trade Mark.

▼ Special reporting to CSM required.

Further information from:
Technical Services Department
ER Squibb & Sons Limited
Squibb House 141-149 Staines Road
Hounslow Middlesex TW3 3JA

Date of preparation June 1990

References

1. Data on file. In trials LIPOSTAT demonstrated an LDL-cholesterol reduction of up to 34% from baseline values (after 8 weeks, 40mg nocte).

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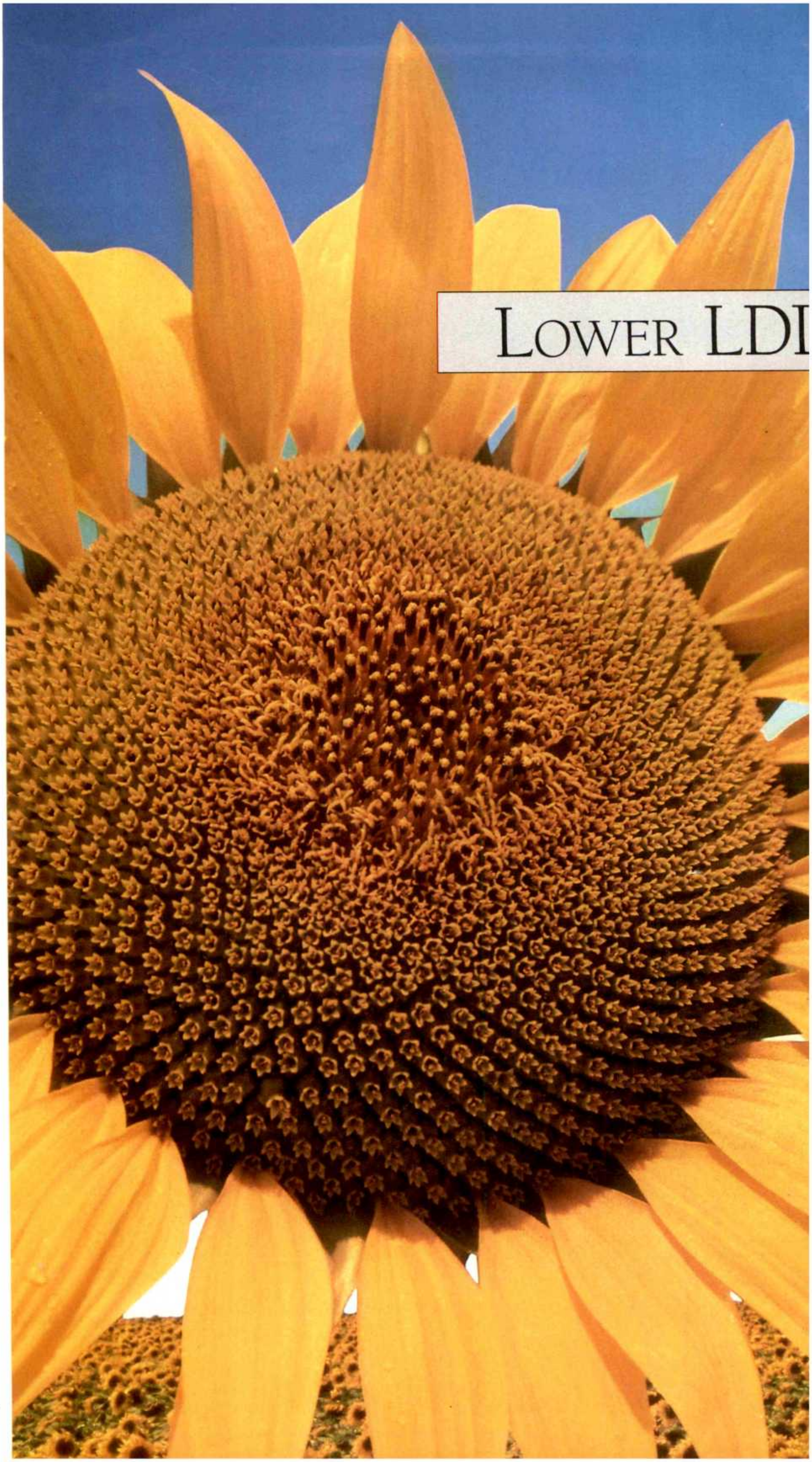
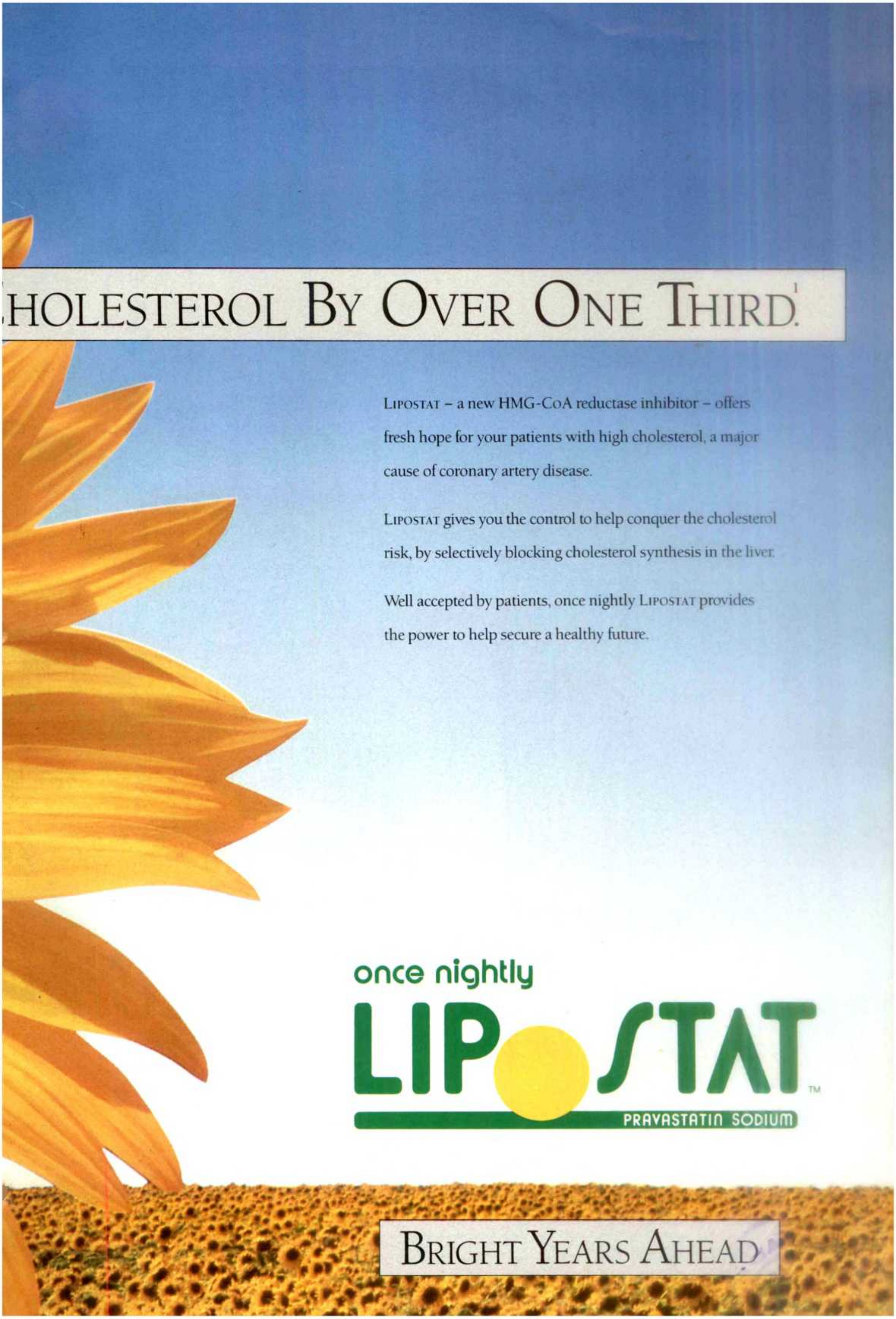




HOLESTEROL BY OVER ONE THIRD.[1]

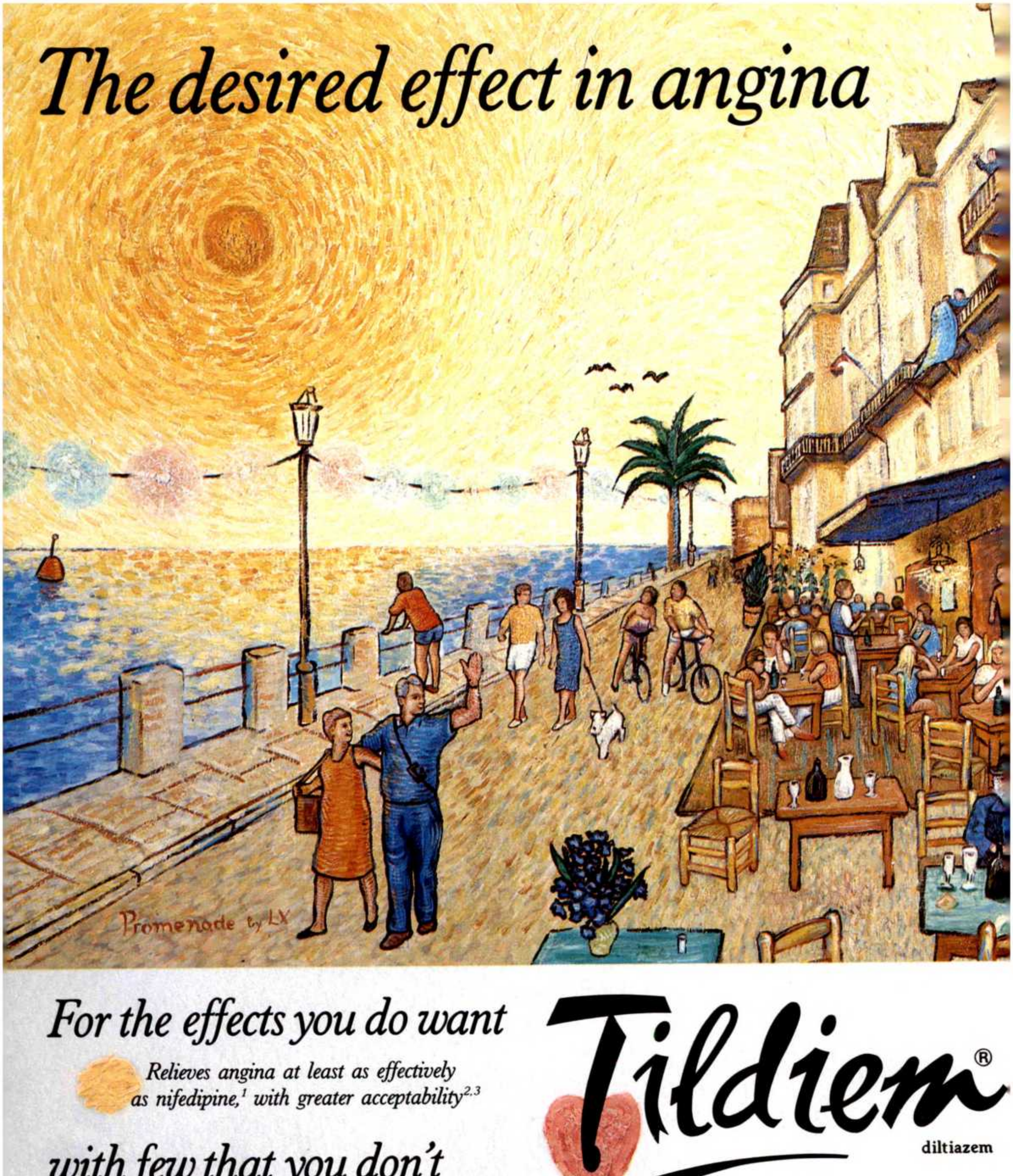
LIPOSTAT – a new HMG-CoA reductase inhibitor – offers fresh hope for your patients with high cholesterol, a major cause of coronary artery disease.

LIPOSTAT gives you the control to help conquer the cholesterol risk, by selectively blocking cholesterol synthesis in the liver.

Well accepted by patients, once nightly LIPOSTAT provides the power to help secure a healthy future.

once nightly
LIPOSTAT™
PRAVASTATIN SODIUM

The desired effect in angina



For the effects you do want

Relieves angina at least as effectively as nifedipine,[1] with greater acceptability[2,3]

with few that you don't

Remarkably few side effects – **headaches** *at placebo levels[4,5]*

Tildiem®

diltiazem

Abbreviated Prescribing Information Presentation: Off-white, biconvex tablets each containing 60mg diltiazem hydrochloride in a modified release formulation. **Indication:** Angina pectoris. **Dosage:** General: Usual adult dose is one tablet (60mg) three times daily. Individual patient response may require up to 360mg daily in divided doses. A total daily dose of 480mg has been used with benefit, especially in patients with unstable angina. Elderly and patients with impaired hepatic or renal function: the recommended starting dose is one tablet (60mg) twice daily. Heart rate should be monitored; if below 50 beats per minute the dose should not be increased. **Contraindications:** Pregnancy and women of child bearing potential. Sick sinus syndrome, left ventricular failure with stasis, second or third degree AV block and severe bradycardia. **Warnings and precautions:** Caution in patients with reduced left ventricular function. Patients with mild bradycardia, first degree heart block or prolonged PR interval should be closely monitored for any worsening of these conditions. Caution should be observed in combination with drugs which may induce bradycardia or those with a hypotensive effect because of a possible additive effect. Plasma [illegible] and theophylline may be slightly raised in the presence of Tildiem. **Side effects:** Ankle oedema, malaise, headache, rash, ho flushes, gastrointestinal disturbances, rarely symptomatic bradycardia, sinoatrial block anc atrioventricular block, vascular skin reactions, raised liver transaminases and isolated case of hepatitis. **Pack size and basic NHS cost:** Blister strips of 10 tablets in packs of 100 table £15.00. **Product licence number:** PL4969/0005. Full prescribing information is availabl on request. Lorex and Tildiem are trade marks. **References 1**. Frishman WH et al, Am Cardiol 1985; **56**: 41H-46H 2. Chaffman M, Brogden RN, Drugs 1985; **29**: 387-454 3 Schroeder JS Mod Medicine 1982; September: 94-116 4. Roberts R, Gibson R, J Cardiovas Pharmacol 1989; **13** (Suppl. 1): S36-S46 5. MDPIT, New Eng J Med 1988; **319** no 7 385-392.

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TI: J50

Br Heart J 1990;64:241-7

Rapid resolution of ST elevation and prediction of clinical outcome in patients undergoing thrombolysis with alteplase (recombinant tissue-type plasminogen activator): results of the Israeli Study of Early Intervention in Myocardial Infarction

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Abstract

Alteplase (recombinant tissue-type plasminogen activator (rt-PA)) was infused within four hours of onset of symptoms in 286 patients with acute myocardial infarction. Delayed coronary angiography was performed 72 hours after admission with coronary angioplasty if indicated. Electrocardiographic monitoring was continuous during the first hour of treatment. The sum of the ST segment elevations (Σ ST) was calculated on electrocardiograms recorded at entry and an hour later. ST elevations resolved rapidly within one hour of treatment in 189 patients and persisted in 97 patients. Rapid resolution of ST elevation correlated with angiographic coronary patency as determined by coronary angiography 72 hours after admission. The patients with rapid resolution of Σ ST had significantly smaller infarcts and a better clinical outcome than the patients with persistent ST elevation. Σ ST values at entry and one hour after treatment had no additional independent predictive value. Rapid resolution of ST elevations in patients undergoing thrombolysis with alteplase was associated with a significantly smaller release of creatine kinase, better preservation of left ventricular function, lower morbidity, and less short and long term mortality. Rapid resolution of Σ ST elevation is an efficient indicator of clinical outcome in groups of patients with acute myocardial infarction undergoing thrombolysis with alteplase.

Thrombolytic treatment in acute myocardial infarction has been shown to be effective in preserving the ventricular ejection fraction[1 2] and reducing short and long term mortality.[3 4] Although 60 to 70% of treated patients can be successfully reperfused,[5] thrombolytic treatment fails in a substantial proportion. These "non-responsive" patients have a significantly high mortality rate[6 7] and may therefore be candidates for emergency angioplasty or coronary artery bypass surgery. We need early reliable indicators to distinguish between patients who will respond favourably to thrombolytic treatment and those who will not.

Coronary angiography immediately after treatment is the most accurate way to document coronary artery patency. However, only a few medical centres can provide timely angiographic evidence of reperfusion for each patient with myocardial infarction. Although resolution of pain and of ST segment elevation have been proposed as markers of myocardial reperfusion,[8-10] it was recently argued that these markers are inadequate in predicting recanalisation of the infarct artery after thrombolytic treatment.[11 12]

The purpose of the Israeli Study of Early Intervention in Myocardial Infarction was to identify possible correlates of clinical outcome in patients with acute myocardial infarction after treatment with alteplase (recombinant tissue-type plasminogen activator (rt-PA)). Intravenous alteplase was given to 289 patients with acute myocardial infarction. The end points included evaluation of left ventricular function, morbidity, and mortality. This report describes the value of rapid resolution of ST segment elevations as an early clinical predictor of patient outcome.

Patients and methods

PATIENTS

The Sheba and Tel Aviv Medical Centres together have more than 2000 beds for acute cases. Both are regional hospitals serving a defined population of over one million. In October 1986 a collaborative study was started to examine the clinical outcome of patients with acute myocardial infarction undergoing early thrombolysis with alteplase and delayed coronary angiography. Patients were recruited via the emergency ward and by the mobile intensive care teams. The study protocol was approved by both institutional committees on human research and all participating patients gave their informed consent.

The entry criteria were age <73 years, severe chest pain for >30 minutes (but no longer than four hours), ST segment elevation of 0·1 mV in at least two contiguous electrocardiographic leads, no left bundle branch block on the qualifying entry electrocardiogram, no congestive heart failure before admission, no history of cardiac surgery, diastolic blood pressure <120 mm Hg, no history of terminal illness, no bleeding predisposition (that is, oral anticoagulant treatment, recent trauma, past bleeding history, or cerebrovascular accident during the past six months).

THROMBOLYTIC REGIMEN

A total dose of 120 mg alteplase (G11035, supplied by Boehringer Ingelheim, West Germany) was given during a 6 hour infusion that consisted of a 10 mg bolus followed by a continuous infusion of 50 mg during the first hour, 20 mg in the second hour, and 10 mg during each of the following four hours.

Concomitantly, a bolus of 5000 IU of heparin was infused followed by 25 000 IU per 24 hours. The dose was adjusted to keep the activated partial thromboplastin time 1 5 to 2 times the baseline. Heparin infusion was continued for at least five days except when patients underwent a successful coronary angioplasty (then heparin treatment was stopped after 24 hours); bled, or were referred for urgent (before discharge) coronary bypass surgery (then heparin was continued until operation). Aspirin (250 mg) was given daily after the first 24 hours and continued during the follow up. Conventional antianginal and anticongestive treatment was used as needed. All patients were treated prophylactically with 2 g of intravenous lignocaine for the first 24 hours.

CORONARY ANGIOGRAPHY AND PERCUTANEOUS TRANSLUMINAL CORONARY ANGIOPLASTY

All patients underwent coronary angiography 72 hours after treatment began unless because of their clinical condition they needed earlier catheterisation. Five patients died before coronary angiography could be done, and in four patients coronary angiography was not performed because of unstable haemodynamic function. Patients with a reduction of >50% in the luminal diameter of the infarct-related artery had angioplasty during the same session unless the infarct artery was a small branch and not important; when the lesion was regarded as unsuitable for angioplasty; or if they were referred for coronary bypass surgery because of three vessel coronary disease, or left main or left main equivalent disease. The clinical response to the thrombolytic treatment (ST resolution as specified below), was not a factor in the decision to perform mechanical revascularisation.

The patency of the coronary arteries was evaluated at each laboratory by a consensus reading of all angiograms by two angiographers who were unaware of the patient's clinical course except for the site of the infarction shown on the electrocardiogram. The severity of coronary artery disease was determined by visual assessment of the reduction in luminal diameter (percentage stenosis) and the Thrombolysis in Myocardial Infarction Trial (TIMI)[13] gradings of perfusion of each coronary artery and its major branches. The success of angioplasty was evaluated visually and improvement was defined as a reduction in lumen stenosis ⩾20% and a final lumen stenosis of <60%.

LEFT VENTRICULAR FUNCTION

During hospital stay each patient underwent three radionuclide studies to assess left ventricular function: the first as soon as possible after admission, but not later than 48 hours (mean (SD) time 22 (17) hours), the second immediately before the 72 hour coronary catheterisation, and the third at discharge.

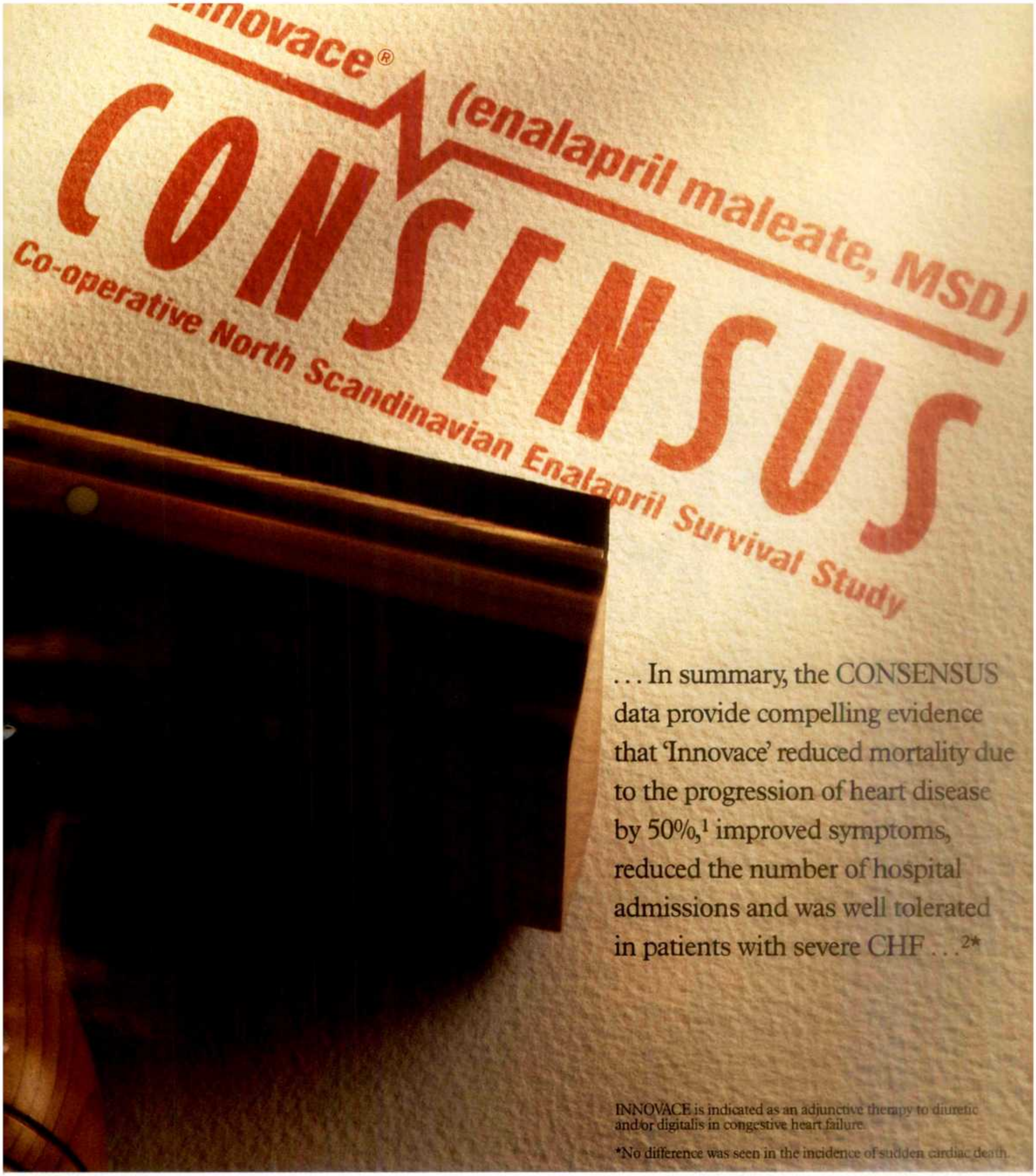
Radionuclide studies were done with an Elscint Apex 415 digital gamma camera in the nuclear cardiology laboratories next to the coronary care unit. A multigated equilibrium blood scan was done in the anterior and 45° left anterior oblique projection with red blood cells labelled in vivo with ^{99}Tc (20 to 25 mCi). The left ventricular ejection fraction was measured in the 45° left anterior oblique projection. A left ventricular time activity curve correlated to background was used to calculate the global ejection fraction semiautomatically. All radionuclide examinations and the left ventricular ejection fraction were assessed by the same two experienced cardiologists who were unaware of the clinical course of the patients examined. For purpose of analysis, the left ventricular ejection fraction at discharge was considered to be zero for the four patients who died before discharge.

PATIENT EVALUATION

All patients stayed in the coronary care unit for at least 24 hours. Patients scored their level of pain from 1 to 10 with the pain level before treatment defined as 10. Significant relief of pain was defined as a reduction of at least 50% within one hour after the start of alteplase infusion. Serial 12 lead electrocardiogram tracings were obtained every three hours during the first 24 hours and at least once daily thereafter until discharge. In addition, a 12 lead electrocardiogram was obtained every 15–30 minutes during the first two hours of treatment or until the ST segment elevation was resolved. Blood samples for creatine kinase were collected every three hours during the first 24 hours. The creatine kinase MB isoenzyme fraction was calculated from the sample in which the creatine kinase concentration was highest. After discharge, patients had follow up clinic visits at 2, 6, and 12 months and once annually thereafter. Surviving patients completed a one year follow up.

CLINICAL DEFINITIONS

Infarction.—The diagnosis of myocardial infarction was based on the occurrence of ischaemic chest pain lasting >30 minutes and accompanied by ST segment elevation of at least 0 1 mV in two contiguous electrocardiographic leads, followed by either an increase in the serum concentration of the creatine



. . . In summary, the CONSENSUS data provide compelling evidence that 'Innovace' reduced mortality due to the progression of heart disease by 50%,[1] improved symptoms, reduced the number of hospital admissions and was well tolerated in patients with severe CHF . . .[2]*

INNOVACE is indicated as an adjunctive therapy to diuretic and/or digitalis in congestive heart failure.

*No difference was seen in the incidence of sudden cardiac death.

RIDGED PRODUCT INFORMATION
er to Data Sheet before prescribing.
DICATIONS
pertension where standard therapy is ineffective
nappropriate. Congestive heart failure (adjunc-
therapy).
SAGE AND ADMINISTRATION
ertension: Initially 5 mg once daily, reduce
rting dose to 2.5 mg if over 65 years, on diuretics
renally impaired. Adjust dose according to
ponse; maintenance usually 10-20 mg once
ly. Maximum dose 40 mg daily. Diuretic-treated
ients – if possible stop diuretic two to three
s before starting 'Innovace'. Resume diuretic
er if required.
gestive heart failure (adjunctive therapy): Initially,
mg daily in hospital under medical supervision,
reasing to the usual maintenance dose of 10-20
once daily according to response.
paired renal function: May require a lower
intenance dose. 'Innovace' is dialysable.
NTRA-INDICATIONS
gnancy – stop therapy if suspected. Hyper-
sitivity to 'Innovace'. Patients reacting with
gioneurotic oedema to previous ACE-inhibitor
tment.

PRECAUTIONS
Assess renal function prior to therapy with 'Innovace' and during therapy where appropriate.
Renal insufficiency; renovascular hypertension; possibility of hypotension especially in ischaemic heart disease or cerebrovascular disease; surgery/anaesthesia.
Combination with antihypertensives may increase hypotensive effect. Sometimes increased blood urea and creatinine and/or cases of renal insufficiency if given with diuretics. Minimises thiazide-induced hypokalaemia and hyperuricaemia. Potassium supplements, potassium-sparing diuretics, and potassium-containing salt substitutes are not recommended. Possible reduced response in Afro-Caribbean patients. Use with caution in breast-feeding mothers. Do not use in aortic stenosis, or outflow tract obstruction. Monitor serum levels of lithium, if lithium salts are given.

SIDE EFFECTS
Dizziness, headache. Others include fatigue, asthenia, nausea, diarrhoea, muscle cramps, rash, dysgeusia, cough.
Less commonly, angioneurotic oedema; other hypersensitivity reactions; renal failure; symptomatic hypotension (especially if volume-depleted); severe hypotension (more likely if severe heart failure); hyperkalaemia; hypokalaemia; increases in liver enzymes and serum bilirubin (usually reversible on discontinuation of 'Innovace'); paraesthesiae; impotence.

BASIC NHS COST
2.5 mg tablets, £10.00 for bottles of 50.
5 mg tablets, £7.86 for 28-day calendar pack.
10 mg tablets, £11.03 for 28-day calendar pack.
20 mg tablets, £13.10 for 28-day calendar pack.

Product licence numbers:
2.5 mg tablets, 0025/0220; 5 mg tablets, 0025/0194; 10 mg tablets, 0025/0195; 20 mg tablets, 0025/0196.

Issued December 1989.

® denotes registered trademark of Merck & Co., Inc., Rahway, NJ, USA.

References
1. CONSENSUS Trial Study Group, *New Engl. J. Med.*, 1987, **316**, 1429.
2. Kjekshus, J., and Swedberg, K., *Amer. J. Cardiol.*, 1988, **62**, 67A-72A.

INNOVACE®
(enalapril maleate, MSD)
Once daily in
congestive heart failure

Merck Sharp & Dohme Limited, Hertford Road
Hoddesdon, Hertfordshire, EN11 9BU

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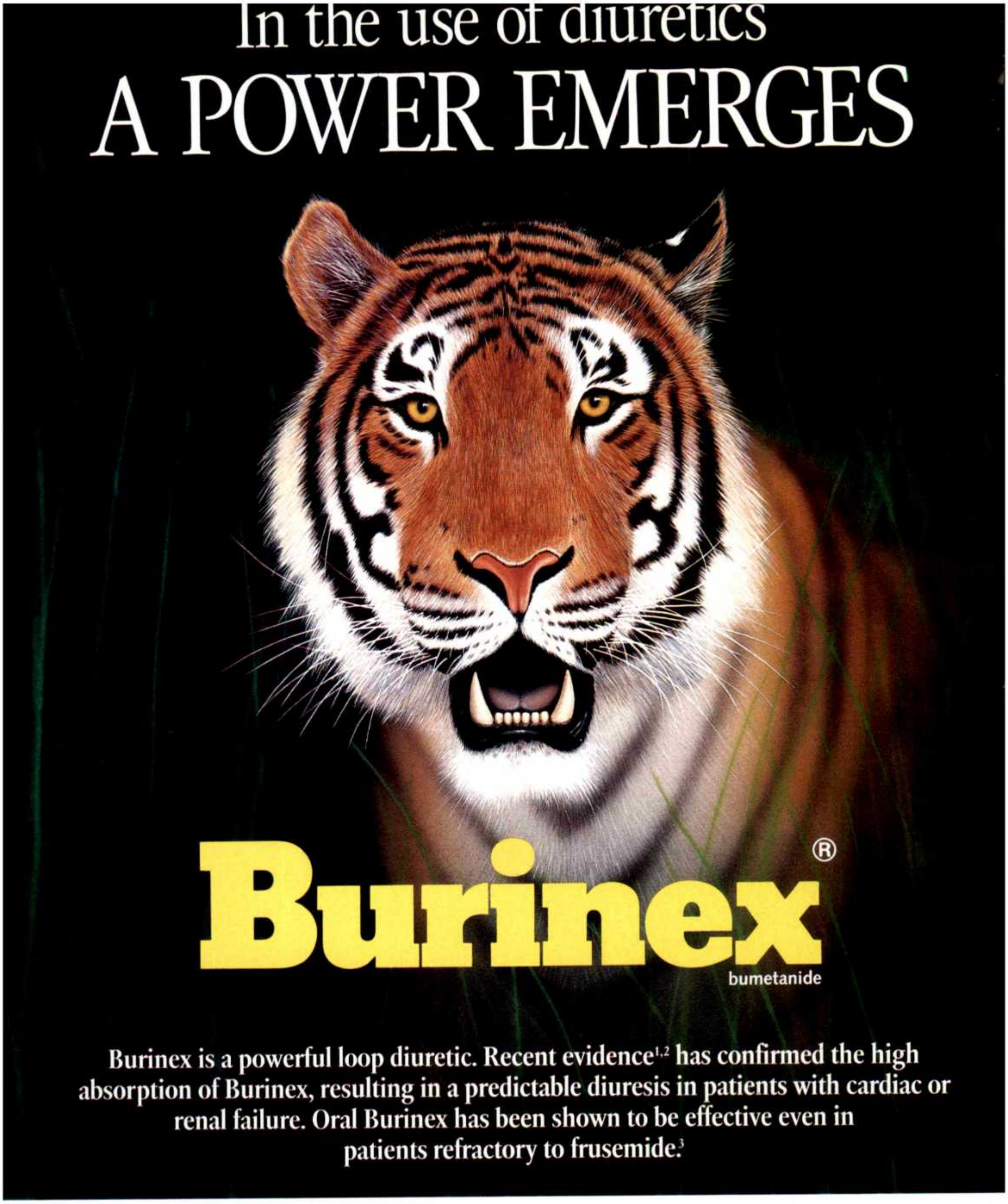

Burinex is a powerful loop diuretic. Recent evidence[1,2] has confirmed the high absorption of Burinex, resulting in a predictable diuresis in patients with cardiac or renal failure. Oral Burinex has been shown to be effective even in patients refractory to frusemide.[3]

Burinex Prescribing Information.
Dosage: Burinex K: 1 to 4 tablets daily as single morning or evening dose. Burinex 1mg tablet: Usual dose 1 tablet daily, increase if necessary. Burinex 5mg tablet: Initial dose 5mg, increasing in 5mg increments if necessary. Burinex liquid: Usual dose 5ml daily, increase if necessary. Burinex injection: In pulmonary oedema, an initial intravenous injection of 1-2mg (2-4ml) should be given. This may be repeated if necessary 20 minutes later. When an infusion is appropriate 2-5mg may be given in 500ml of infusion fluid, over 30-60 minutes. For intramuscular injection, a dose of 0.5-1mg (1-2ml) should be given initially and the dose then adjusted to the diuretic response. **Presentation:** Burinex K: Each tablet contains bumetanide 0.5mg and potassium chloride 573mg. Burinex 1mg tablet: Each tablet contains bumetanide 1mg. Burinex 5mg tablet: Each tablet contains 5mg bumetanide. Burinex liquid: Each 5ml contains 1mg bumetanide. Burinex injection: 2ml, 4ml and 10ml ampoules containing 0.5mg bumetanide/ml ie., 1mg, 2mg and 5mg bumetanide. **Indication:** Treatment of oedema. **Side Effects, Precautions and Contra-Indications:** Burinex and Burinex K are contra-indicated in hepatic coma, severe electrolyte depletion and severe progressive renal failure. As with other diuretics, Burinex and Burinex K should not be administered concurrently with lithium salts. Inappropriate excessive diuresis may result in hypovolaemia and circulatory collapse. The use of digitalis in cases of electrolyte disturbance may lead to digitalis toxicity. Concurrent antihypertensive or antidiabetic therapy may require adjustment. The use of Burinex or Burinex K during the first trimester of pregnancy should be avoided. Side effects such as raised serum uric acid, skin rashes, muscular cramps and thrombocytopenia may occur. Burinex K is contra-indicated in combination with potassium sparing agents, and should be discontinued immediately if signs or symptoms of bowel ulceration occur. **Product Licence Number:** Burinex K: 0043/0027, Burinex 1mg tablet: 0043/0021, Burinex 5mg tablet: 0043/0043, Burinex liquid: 0043/0075, Burinex injection: 0043/0060. **Basic N.H.S. Price:** Burinex K: £21.26/500, Burinex 1mg tablet: £6.27/100, Burinex 5mg tablet: £28.62/100. Burinex liquid: £3.41/bottle of 150ml. Burinex injection: (packs of 5 ampoules) 2ml ampoules: £2.06, 4ml ampoules: £3.56, 10ml ampoules: £7.47.

References

1. Cook, J.A. et al., Clin. Pharmacol. Ther., **44**, 487, 1988.
2. Lau, H.S.H. et al., Clin. Pharmacol. Ther., **39**, 635, 1986.
3. Pines, A. et al., Br. J. Clin. Pract., **28(9)**, 311, 1974.

LEO

Further information available on request from:
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Princes Risborough, Aylesbury, Bucks HP17 9RR.

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kinase MB fraction of >5%, or the appearance of new Q waves not present on the initial electrocardiogram. Abnormal Q waves were those lasting $\geq$ 0·03, at least 4 mm deep, and >25% of the height of the ensuing R wave all in leads other than aVR or V1.

Rapid resolution of ST segment elevation.—As in earlier reports,[13 14] we calculated the sum of ST segment elevations (Σ ST) on the electrocardiograms recorded at admission and 1 hour after treatment. Electrocardiograms were evaluated within the first 24 hours after admission by two independent observers, one from the coronary care unit treating the patient and one observer who was not involved in the care of these patients. In cases of disagreement, a third opinion was sought. Resolution of ST segment elevation was defined as a decrease of at least 50% of the baseline Σ ST elevation.

Patency.—A TIMI grade of 2 or 3 signified patency of the infarct related coronary artery. Occlusion of the infarct-related artery was defined as TIMI grade 0 or 1.[15]

Clinical prognostic groups.—Patients were categorised as having a first infarction in the anterior or inferior wall or a history of infarction irrespective of the location of the current infarction.

STATISTICAL ANALYSIS

Group data are expressed as mean (SD) for continuous variables or as rates (percentage) for categorical variables. For continuous variables we used the Mann-Whitney rank sum test for univariate comparisons of differences between patients with and without rapid resolution of Σ ST because the variance in some of the variables was unequal. For categorical variables, we used the χ^2 or, when appropriate, Fisher's exact test for 2 × 2 tables. Logistic regression analysis (Biomedical Computer Programs, University of California, Berkley CA-BMDP program LR) was performed wth rates of each of the following six outcomes as the dependent variable: immediately abnormal (<50% ejection fraction) left ventricular function, abnormal left ventricular function at discharge, congestive heart failure at discharge, Q wave infarction, angiographic occlusion of the coronary artery, and mortality.

The effect of the following independent risk variables related to Σ ST change on the outcome variables was analysed: persistent ST elevation (<50% reduction in Σ ST) for at least one hour after treatment began, Σ ST at admission, Σ ST one hour after the start of treatment, and the ratio of the two Σ ST values as continuous variables. Additional independent risk variables were: persistence of chest pain for at least one hour after the start of treatment, number of diseased coronary vessels, clinical prognostic group, age, sex, and smoking. The independent risk ratios (with 95% confidence intervals) associated with each of the independent variables were derived from the logistic coefficients.

Table 1 Baseline characteristics of patients with rapid ST elevation and without

Characteristic	*Rapid reduction of ST elevation n=189 (100%)*	*Persistent elevation of ST elevation n=97 (100%)*	*p Value*
Male (%)	160·0 (84·7)	83·0 (83·0)	0·97
Age (mean (SD))	56·6 (9·5)	58·6 (8·9)	0·09
Anterior infarction (%)	68·0 (36·0)	44·0 (45·4)	0·05
Inferior infarction (%)	97·0 (51·3)	28·0 (28·9)	
Previous infarction (%)	24·0 (12·4)	25·0 (25·7)	
Single vessel disease (%)*	87·0 (46·0)	41·0 (42·3)	0·94
Mean (SD) systolic BP	125·7 (22·1)	127·2 (28·2)	0·94
Mean (SD) time to treatment (min)	123·7 (51·2)	112·4 (43·6)	0·053†

*Excluding five patients who died before coronary angiography was performed and two patients who did not have coronary angiography because their haemodynamic condition was unstable.
BP, blood pressure
†ANOVA test for unequal variances.

Results

PATIENTS' BASELINE DATA

Two hundred and eighty six patients were eligible for thrombolytic treatment. Of these, 169 were admitted via the emergency ward and 117 patients were brought in by the mobile intensive care units. The mean (SD) time from onset of symptoms to treatment was 2·0 (0·6) hours.

Table 1 shows the demographic and clinical characteristics of patients at entry. In 189 patients (66·0%) we saw rapid resolution of ST segment elevation, whereas in 97 patients (33·9%) ST segment elevation persisted despite an hour of alteplase infusion. The two groups were generally comparable. In the group of patients with rapid resolution of ST elevation, however, anterior wall infarction was less common, previous infarction was more common, and the time from onset of symptoms to the start of treatment was longer (124 (51) *v* 112 (44) min respectively, p = 0·053). In the patients with anterior wall infarction with rapid resolution of ST elevation and in those without, baseline Σ ST elevation was 18·3 (9·4) and 22·3 (12·8) respectively (p = NS). In those with inferior wall infarction, baseline Σ ST elevation was 8·4 (4·2) in those with rapid resolution of ST elevation and 10·5 (6·8) in those without (p = NS). The baseline Σ ST elevation in patients with previous infarction was similar in patients with rapid resolution of ST elevation and those without (11·8 (5·5) *v* 15·3 (9·9), p = NS).

In 10 patients the initial clinical picture of myocardial infarction was not confirmed by an increase in the activity of the MB isoenzyme fraction of creatine kinase or the development of new Q waves on their electrocardiograms. All 10 patients showed rapid resolution of ST elevation. We present the results for the total group, because exclusion of these patients from analysis did not affect the differences between the patients with rapid ST resolution and the patients with persistent ST elevation.

PAIN RESOLUTION

Pain resolved quickly in 153 (85·9%) of 178 patients with rapid resolution of ST elevation and in only 21 (22·3%) of 94 patients with persistent ST elevation (the change in pain was not recorded in 11 patients with rapid ST resolution and in three patients with persistent

ST elevation) (p < 0·0001). The outcome of the 25 patients with rapid resolution of ST elevation but no pain resolution resembled that in the 153 patients who had resolution of both pain and ST segment elevation. The 21 patients with abrupt pain relief but no ST resolution resembled the 73 patients with persistent pain and ST elevation (data not shown). Consequently, data are categorised by the presence or absence of rapid resolution of ST segment elevation, irrespective of pain resolution.

MYOCARDIAL ENZYME KINETICS

Rapid resolution of ST elevation was associated with significant limitation of infarct size as reflected by a smaller creatine kinase peak (fig 1) and total release of creatine kinase over the first 24 hours (sum of all samples measured as area under the curve) (table 2). Total 24 hour creatine kinase release was significantly lower in patients with rapid resolution of ST elevation in all prognostic clinical groups than in patients with persistent ST elevation (table 2).

LEFT VENTRICULAR FUNCTION

Patients with rapid ST resolution and those without differed markedly in the preservation of their left ventricular function. Both the proportion of patients whose left ventricular ejection fraction was normal immediately after admission (> 50%) and at discharge (fig 2) and the mean ejection fraction (table 3) were significant higher in the group with rapid resolution of ST elevation. This difference was more prominent in the patients with anterior wall infarction than in those with inferior wall infarction or old infarction. However, left ventricular function at admission and at discharge was better in patients with inferior wall infarction than in the other two groups. The mean left ventricular ejection fraction determined by ventriculography during cardiac catheterisation on the third day after admission was also significantly higher in the patients with rapid ST resolution (59 (13) *v* 49 (13), p < 0·0001).

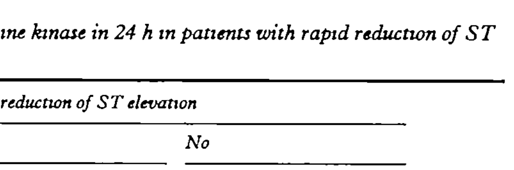

Figure 1 Peak serum concentration of creatine kinase during the first 24 hours in patients with rapid resolution of ST elevation and without

Table 2 Total release of creatine kinase in 24 h in patients with rapid reduction of ST segment elevation and without

	Rapid reduction of ST elevation				
	Yes		*No*		
Patient group	*n*†	*IU (SD)*	*n*†	*IU (SD)*	*p Value**
Total	173	5248 (4265)	84	10 553 (7762)	<0 0001
Anterior infarction	65	6014 (4790)	37	13 408 (9441)	<0 0001
Inferior infarction	88	4939 (3973)	25	7691 (4382)	0 0002
Previous infarction	20	4118 (3354)	22	9002 (6062)	0 0015

*Mann-Whitney rank sum test.
†Excluding 16 of 189 patients with rapid reduction of ST elevation and 13 of the 97 patients with persistent ST elevation. In these 29 patients incomplete sampling prevented calculation of the total release of creatine kinase.

CLINICAL OUTCOME

The proportion of patients who underwent mechanical revascularisation procedures was similar in patients with rapid resolution of ST elevation and in those without. Thus of the 189 patients with rapid resolution of ST elevation, 124 (65·6%) had angioplasty or bypass procedures, and 52 (53 6%) of the 97 patients with persistent ST elevation underwent mechanical revascularisation.

Coronary angiography was performed 4·0 (1·7) and 4·1 (2·1) days respectively after enrolment of the patients with rapid ST resolution and the patients with persistent ST elevation. Coronary angioplasty was performed 4·7 (1·4) and 3·8 (2·0) days respectively after enrolment in the patients with rapid ST resolution and the patients with persistent ST elevation (p = NS). In both groups, about a quarter of the coronary interventions were performed within the first 72 hours. Coronary angioplasty was successful in 96% of the patients with rapid ST resolution and 94% of the patients with persistent ST elevation.

At discharge, patients with rapid resolution of ST elevation had a better outcome in terms of a significantly lower incidence of congestive heart failure (defined as requirement for digoxin or diuretics at discharge) and a higher incidence of non-Q wave infarction (fig 2 and table 4). This difference was more pronounced in the patients with anterior infarctions.

MORTALITY

Thirteen patients (4·5%) died within 60 days of infarction; eleven of these died in hospital (3 8%). Patients with rapid resolution of ST elevation had a lower 60 day mortality (3/189 *v* 10/97, p = 0·0015). Of the 10 patients with persistent ST elevation, one patient with anterior wall infarction died of ventricular fibrillation 10 minutes after treatment began. In the remaining nine patients (six with anterior wall infarction and three with inferior infarction) cardiogenic shock developed, and in two patients a ruptured myocardium was eventually found. Two of the three patients who responded to the alteplase infusion with rapid resolution of ST elevation had an anterior wall infarction and the third had an inferior wall infarction. In all three patients acute reinfarction with cardiogenic shock developed—in two within hours of coronary angiography and angioplasty.

Five additional patients died between 2 and 24 months after infarction (mean follow up time of 24·3 (3·4) months). Three of these patients originally did not show ST segment resolution: two patients died two and three months later of reinfarction and cardiogenic shock and the third died three months later of anaphylactic shock (non-cardiac death). Two additional patients who initially responded

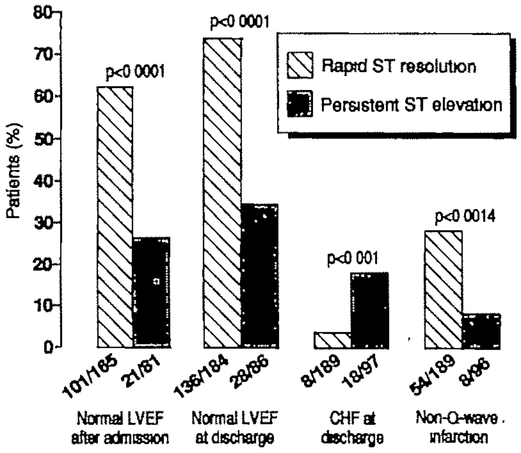

Figure 2 Clinical outcome in patients with rapid resolution of ST elevation and without. LVEF, left ventricular ejection fraction; CHF, congestive heart failure.

Table 3 Left ventricular ejection fraction in patients with rapid reduction of ST segment elevation and without

	Rapid reduction of ST elevation				
	Yes		*No*		
Patient group	*n*	*LVEF* (SD)*	*n*	*LVEF (SD)*	*p Value**
Total population:					
Immediate LVEF	165†	52 (13)	81†	41 (15)	<0 0001
Discharge LVEF	184†	55 (12)	86†	44 (14)	<0 0001
Anterior wall infarction					
Immediate LVEF	53	46 (13)	37	33 (11)	<0 0001
Discharge LVEF	66	53 (14)	40	39 (14)	<0 0001
Inferior wall infarction:					
Immediate LVEF	91	57 (10)	25	55 (11)	0·44
Discharge LVEF	96	58 (9)	26	53 (12)	0 052
Old infarction					
Immediate LVEF	21	46 (15)	19	38 (12)	0 09
Discharge LVEF	22	49 (16)	20	41 (11)	0 09

*Mann Whitney rank sum test

†Excluding 40 immediate and 16 discharge radionuclide ventriculographies that were missing or were not suitable for interpretation The discharge LVEF was nominally 0 in the 11 patients who died before discharge.

LVEF, left ventricular ejection fraction (%).

Table 4 Clinical outcome in patients with rapid reduction of ST elevation and without

	Rapid reduction of ST segment elevation		
Characteristic	*Yes (%)*	*No (%)*	*p Value*
Congestive heart failure			
Total population	8/189 (4 2)	18/97 (18·5)	<0 001
Anterior infarction	3/68 (4 4)	8/44 (16 6)	0 017
Inferior infarction	2/97 (2 0)	2/28 (7·1)	0·21
Previous infarction	3/24 (12 5)	8/25 (32 0)	0·10
Non-Q wave infarction:			
Total population*	54/189 (28 6)	8/96 (8·3)	<0 001
Anterior infarction	24/68 (35 3)	1/43 (2·3)	<0 0001
Inferior infarction	25/97 (25 8)	5/28 (17 9)	0·54
Previous infarction	5/24 (20 8)	2/25 (8 0)	0 19

*Excluding one patient who died within 10 minutes of the start of treatment and in whom Q wave infarction did not develop

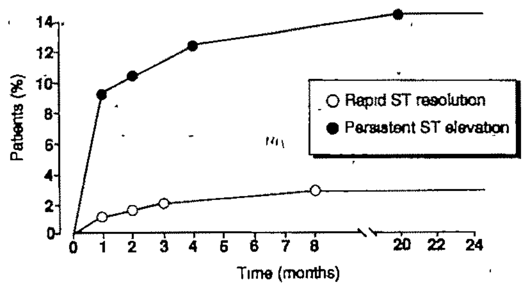

Figure 3 Cumulative mortality (%) of patients with rapid resolution of ST elevation and without.

with rapid resolution of pain and ST segment elevation died: one in the third month of a ruptured septic aortic aneurysm and the other after eight months of hepatic malignancy. Thus overall mortality among the 97 patients with persistent ST elevation was higher than that in the 189 patients with rapid resolution of ST elevation (13·4% *v* 2·6%, $p < 0·0007$) (fig 3).

CLINICAL MARKERS AND ANGIOGRAPHIC PATENCY

Table 5 shows the correlation between the clinical response to thrombolytic treatment and patency of the infarct artery during coronary angiography after three days. At that time the patency rate of the infarct artery was higher in patients with rapid resolution of ST elevation (86·6% *v* 76 1%, $p = 0·04$).

In contrast with the strong association between a favourable clinical outcome and rapid resolution of ST segment elevation, the patency of the infarct artery at 72 hours was not associated with less creatine kinase release, preservation of left ventricular function, or lower morbidity after alteplase thrombolysis (table 6). Total mortality among angiographically assessed patients was lower in those with a patent infarct artery (eight of 231 *v* 5 of 46, $p = 0·01$). Even when the five deaths in patients who did not survive to angiography were included, persistent ST elevation was more common than occlusion of the infarct artery among patients who died (13 patients with persistent ST elevation compared with five patients with an occluded infarct artery among 18 who died).

MULTIVARIATE ANALYSIS OF FACTORS AFFECTING THE CLINICAL OUTCOME VARIABLES

Preliminary logistic regression analysis indicated that there were four measures related to the change in the ST elevation after treatment—that is, the continuous variables Σ ST at admission; Σ ST one hour after treatment initiation; ratio of this value to the admission Σ ST; or the categorical definition of <50% reduction of Σ ST from admission level (persistent ST elevation)—but only the last variable was strongly associated with all outcome variables and excluded the other three variables from the model. Consequently, the final analysis was done with persistent Σ ST elevation alone.

The analysis evaluated the effect of each risk variable on each of the outcome variables after its association with other risk variables is taken

Table 5 Patency rate (%) of the infarct related artery at 72 hour coronary angiography and presence of rapid reduction of ST elevation according to site of infarction

	Rapid reduction of ST segment elevation		
	Yes	*No*	*p Value*
Total population*	86 6	76·1	0 043
Anterior infarction	93 9	80 5	0 035
Inferior infarction	81 4	85 7	0 41
Previous infarction	86 9	55 5	0 0224†

*Excluding five patients who died before coronary angiography and four patients in whom coronary angiography could not be performed because they were haemodynamically unstable

†Fisher's exact test.

Table 6 Clinical outcome in patients with a patent and an occluded infarct artery

	Infarct artery patent		*Infarct artery occluded*		
	n	*Units (SD)*	*n*	*Units (SD)*	*p Value*
Creatine kinase peak (IU)	231	1260 (1271)	46	1231 (1068)	0·88
Creatine kinase AUC*	212	6890 (6294)	40	6816 (4997)	0·94
Immediate LVEF (%)	202	48 (14)	42	48 (15)	0·98
Discharge LVEF (%)	225	52 (14)	41	50 (12)	0·34
Congestive failure (%)	13/230 (5·6)		5/45 (11·1)		0·15
Non-Q wave infarction (%)	54/231 (23·4)		9/46 (19·6)		0·71
Total mortality (%)	8/231 (3·4)		5/46† (10·8)		<0·05‡

*AUC, area under the curve representing the total release of creatine kinase during the first 24 hours after admission.
†Excluding five patients who died before coronary angiography
‡Fisher's exact test
LVEF, left ventricular ejection fraction.

into account. For instance, the group with rapid resolution of ST segment elevation contained a greater proportion of patients with inferior wall infarction, which is itself associated with a more favourable outcome. Multivariate analysis gave a net risk ratio (relative risk of the group with rapid ST resolution and those without) for each outcome, which took into account the effect of the initial advantage. This analysis indicated that after accounting for all other risk variables, persistent ST elevation was associated with an independent, highly significant increased risk of all outcome variables, including infarct artery occlusion rate. It is noteworthy that abrupt resolution of pain had no independent predictive value for any of the outcome variables. Also, the value of the admission Σ ST had no additional independent predictive value for clinical outcome.

Factors that had additional prognostic effect on left ventricular function included the clinical prognostic group, presence of three vessel coronary artery disease, age, and sex. Factors affecting congestive heart failure included clinical prognostic groups and age. In addition to rapid resolution of ST elevation, only the patient's prognostic group was predictive of mortality.

Discussion

The most conclusive evidence of reperfusion is the angiographic demonstration of recanalisation of an infarct related artery shown to be occluded during pre-treatment coronary angiography. However, to minimise the delay before treatment and to conserve costs most current thrombolytic protocols no longer include pre-treatment catheterisations.[16–18] Our medical centres, like many others, cannot routinely support immediate coronary angiography for all patients treated by thrombolysis. Moreover, recent results of the TIMI phase II,[16] TAMI (Thrombolysis and Angioplasty in Myocardial Infarction),[17] and the European Cooperative[18] trials suggest that after successful thrombolysis, immediate coronary angiography and angioplasty may not be necessary. When post-thrombolytic coronary angiography is deferred for a few days, the patency rate reflects both the spontaneous and the (pharmacologically) induced coronary thrombolysis. Thus without early angiographic evidence of reperfusion, we are left with its clinical surrogates to identify patients with an unfavourable prognosis.

Our data indicate that the rapid resolution of ST segment elevation was significantly associated with a more favourable clinical outcome. In part, this more favourable outcome may have been related to the better baseline clinical characteristics in this group. However, even after the effect of this initial advantage was accounted for by multivariate analysis, this early clinical sign of reperfusion was significantly associated with a smaller infarct, as evidenced by a smaller release of creatine kinase, better preservation of left ventricular function, and significantly lower morbidity and mortality. Moreover, resolution of ST segment elevation was a better predictor of clinical outcome, including mortality, than was the patency rate determined by coronary angiography three days after admission (table 6). Multivariate analysis showed that the better outcome in the patients with rapid ST resolution was independent of their better baseline status (that is the lower rate of old or anterior wall infarctions or both as well as the initially lower Σ ST). Our analysis indicates that the categorical variable of 50% resolution from the initial Σ ST elevation to the one hour Σ ST value was also superior to the change in Σ ST as a continuous variable.

These findings are consistent with those of the open-label phase of the TIMI Trial in which a decline in ST elevation from entry to two hours correlated with better left ventricular function in patients with acute myocardial infarction treated by thrombolysis.[19] ST segment elevation resolved more rapidly in patients treated with streptokinase than in the control group.[13 20] Also, ST segment elevation decreased significantly within one and three hours after treatment in patients with confirmed angiographic reperfusion.[14 21 22]

Despite this evidence, it was recently argued that clinical markers of reperfusion were inadequate predictors of early recanalisation of the infarct artery after thrombolytic treatment.[11] In our patients, rapid resolution of ST elevation was associated with a higher patency rate in the infarct-related artery three days after treatment began. The difference in the patency rate between the two patient groups, though significant, was small (86·7 v 76·9%). In view of this small difference in patency between the two groups, how could resolution of ST elevations predict the clinical outcome of our patients who were treated with thrombolysis? Moreover, how can the high patency rate in the group with persistent ST elevation be reconciled with their unfavourable outcome?

It could have been argued that angiography 72 hours after thrombolysis does not reflect the patency rate when alteplase infusion ended and that in patients with persistent ST elevation an earlier angiography would have detected lower patency rates. However, the patency rate (76%) we saw (at 72 hours) in patients with persistent ST elevation was significantly higher than the 40% rate reported in patients with a three day old myocardial infarction who were not treated by thrombolysis.[23] Thus coronary thrombolysis was successful in a substantial proportion of our patients with persistent ST elevation. But perhaps reperfusion was more effective in patients with rapid ST resolution than in those with persistent ST elevation. The effectiveness of the reperfusion may have been influenced by additional factors such as the existence of subtotal coronary occlusion or good collateral circulation, the rate and promptness of coronary artery recanalisation, and the residual stenosis in the infarct artery.

Thus rapid resolution of ST segment elevation may indicate a more effective reperfusion leading to a better clinical outcome. This possibility is supported by the fact that in the multivariate analysis rapid resolution of ST segment elevation was associated with a significantly favourable outcome with respect to all outcome variables after the effect of all baseline variables was accounted for. When ST segment elevation persisted despite one hour of alteplase thrombolysis, reperfusion was probably less effective even when angiographic patency was eventually seen. Because mechanical revascularisation procedures were performed to a similar extent in both groups, this factor could not have accounted for the better outcome of patients with rapid resolution of ST elevation.

Abrupt resolution of pain, though it was much more common among patients with rapid ST resolution, did not have any additional predictive power when combined with rapid resolution of ST elevation. However, as a sign of reperfusion, pain resolution is not very specific, partly because of the use of analgesics. Nevertheless, the outcome in patients with rapid resolution of ST elevation but persistent ischaemic pain was similar to that in patients with resolution of both pain and ST elevation.

As a general strategy, immediate post-thrombolytic coronary angiography has profound practical limitations. Round-the-clock catheterisation laboratories are available in only a few medical centres. So after thrombolytic treatment in myocardial infarction there is a need for early, bedside, clinical measures to evaluate patients' response to treatment. Despite the strong association of rapid ST resolution with a more favourable outcome, it is limited in the identification of high risk patients who may need more vigorous treatment. This was shown by the finding that among patients with depressed left ventricular function, congestive heart failure, or Q wave infarction, >50% still had rapid resolution of ST elevation.

While rapid resolution of ST elevation may be a less effective indicator for the individual patient it is still a predictor of a better outcome and in patients treated by thrombolysis it can be used as a measure of the effectiveness of treatment in different subgroups.

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1 Spann JF, Sherry S, Carabello A, *et al.* Coronary thrombolysis by intravenous streptokinase in acute myocardial infarction· acute and follow-up studies *Am J Cardiol* 1984,53 655–61
2 Koren G, Weiss AT, Hasin Y, *et al.* Prevention of myocardial damage in acute myocardial ischemia by early treatment with intravenous streptokinase. *N Engl J Med* 1985;313 1384–9.
3 Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico (GISSI) Effectiveness of intravenous thrombolytic treatment in acute myocardial infarction *Lancet* 1986,i·397–401
4 Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico (GISSI) Long-term effects of intravenous thrombolysis in acute myocardial infarction final report of the GISSI study *Lancet* 1987,ii 871–4
5 Marder VJ, Sherry S Thrombolytic therapy, current status *N Engl J Med* 1988,318 1512–20.
6 Kennedy JW, Ritchie JL, Davis KB, Stadius ML, Maynard C, Fitz JK. The western Washington randomized trial of intracoronary streptokinase in acute myocardial infarction. A 12-month follow-up report. *N Engl J Med* 1985,312.1073–8
7 Topol EJ, Califf RM, Kereiakes DJ, George BS Thrombolysis and Angioplasty in Myocardial Infarction (TAMI) trial *J Am Coll Cardiol* 1987,10 65B–74B.
8 Ganz W, Geft I, Shah PK, *et al.* Intravenous streptokinase in evolving acute myocardial infarction *Am J Cardiol* 1984,53 1209–16
9 Rentrop P, Blanke H, Karsch KR, Kaiser H, Kostering H, Leitz K. Selective intracoronary thrombolysis in acute myocardial infarction and unstable angina pectoris *Circulation* 1981,63 307–17
10 Mathey DG, Kuck KH, Tilsner VJ, Krebber HJ, Bleifeld W. Non surgical coronary artery recanalization in acute transmural myocardial infarction *Circulation* 1981;63·489–97
11 Kircher BJ, Topol EJ, O'Neill WW, Pitt B Prediction of coronary artery recanalization after intravenous thrombolytic therapy *Am J Cardiol* 1987;59 513–5.
12 Ross AM, TIMI investigators Electrocardiographic and angiographic correlations in myocardial infarction patients treated with thrombolytic agents a report from the NHLBI thrombolysis in myocardial infarction (TIMI) trial *J Am Coll Cardiol* 1985,5 495A.
13 Blanke H, Scherff F, Karsch KR, Levine RA, Smith H, Rentrop P Electrocardiographic changes after streptokinase-induced recannalization in patients with acute left anterior descending artery obstruction *Circulation* 1983,68 406–12
14 Von Essen R, Schmidt W, Uebis R, *et al* Myocardial infarction and thrombolysis Electrocardiographic short term and long term results using precordial mapping *Br Heart J* 1985,54 6–10.
15 The TIMI study group. The Thrombolysis in Myocardial Infarction (TIMI) trial Phase I findings *N Engl J Med* 1985,312:932–6
16 The TIMI Research Group Immediate vs delayed catheterization and angioplasty following thrombolytic therapy for acute myocardial infarction TIMI II A results. *JAMA* 1988;260.2849–58.
17 Topol EJ, Califf RM, George BS, *et al* A randomized trial of immediate versus delayed elective angioplasty after intravenous tissue plasminogen activator in acute myocardial infarction. *N Engl J Med* 1987;317 581–8
18 Simoons ML, Arnold AE, Betriu A, *et al.* Thrombolysis with tissue plasminogen activator in acute myocardial infarction: no additional benefit from immediate percutaneous coronary angioplasty *Lancet* 1988,i.198–203.
19 Bren GB, Wasserman AG, Sheehan FH, Forman S, Dodge HT, Ross AM, TIMI investigators Electrocardiographic evolution during acute myocardial infarction as a correlate of left ventricular function outcome *Circulation* 1985,72 (suppl III) III–419
20 Anderson JL, Marshall HW, Bray BE, *et al* A randomized trial of intracoronary streptokinase in the treatment of acute myocardial infarction *N Engl J Med* 1983, 308 1312–8
21 Krucoff MW, Green CE, Satler LF, *et al.* Non invasive detection of coronary artery patency using continuous ST-segment monitoring. *Am J Cardiol* 1986,57:916–22.
22 Hogg KJ, Hornung RS, Howie CA, Hockings N, Dunn FG, Hillis WS. Electrocardiographic prediction of coronary artery patency after thrombolytic treatment in acute myocardial infarction use of the ST segment as a non-invasive marker *Br Heart J* 1988,60·275–80
23 De Feyter PJ, van Eenige MJ, van der Wall EE, *et al* Effects of spontaneous and streptokinase-induced recanalization on left ventricular function after myocardial infarction. *Circulation* 1983;67 1039–44.

Br Heart J 1990,64:248–50

Does blood rheology revert to normal after myocardial infarction?

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Abstract

After myocardial infarction there is an acute deterioration of the flow properties of blood. The present study was designed to test whether the abnormality persists. Blood and plasma viscosity, red cell aggregation and deformability, haematocrit, erythrocyte sedimentation rate, white cell count, cholesterol, and triglycerides were measured in 51 patients who had had a myocardial infarction 5·4 (mean) years before. Results in patients and controls were compared and matched pairs with identical cardiovascular risk factors were also selected. Blood viscosity and red cell aggregation were increased and red cell deformability was decreased in the 51 patients. The abnormalities were independent of the interval since infarction and persisted for years.

The rheological abnormalities present after myocardial infarction are at least partly independent of the acute event and acute phase reactions. They contribute to the reduced perfusion of the microcirculation of the heart.

Blood rheology represents the viscous component of the total peripheral resistance.[1] Its influence on perfusion in various vascular beds increases when the vasomotor reserve is limited.[2] The main determinants of blood viscosity (a crude indicator for the flow properties of blood) are: haematocrit, plasma viscosity, red cell aggregation, and red cell deformability.[1]

After acute myocardial infarction the blood becomes more viscous.[3] If this is a transient acute phase reaction its effect on the perfusion of the heart will not be important; but persistent rheological abnormalities could contribute to the hypoperfusion of the myocardium and might be of pathophysiological importance.[4,5] We tested haemorrheological variables in patients years after the acute phase of myocardial infarction.

Patients and methods

PATIENTS

We studied 51 (six women and 45 men) consecutive patients aged 39–60 (mean (SD), 54·9 (5·0)) admitted to our rehabilitation unit with confirmed (clinical signs, electrocardiogram, enzymes) acute myocardial infarction from 2 months to 20 years before (mean 5·4) (table 1). We excluded those aged >60 years, those with malignancies or acute or chronic inflammatory diseases, and those taking medications with effects on rheological variables. We used the same criteria to select a control group of 20 patients at the same clinic without a history of infarction.

METHODS

Venous blood was drawn according to a standardised protocol and anticoagulated with 12·5 U/ml lithium heparin. Immediately afterwards the following tests were carried out in triplicate: (*a*) blood viscosity at 37°C and defined shear rates measured by the LS 30 rotational viscometer (Contraves)[6]; (*b*) blood viscosity (as above) at a standardised haematocrit of 45%[7]; (*c*) haematocrit (microhaematocrit centrifuge); (*d*) plasma viscosity at 37°C (Coulter-Harkness viscometer)[8]; (*e*) red cell aggregation by a newly developed technique where the difference of the maximum reading of blood viscosity at very low (0·7 s^{-1}) shear rate and the value 45 seconds after maximum is taken as a measure of the energy needed to disaggregate red cells[9]; (*f*) red cell deformability measured as blood viscosity at high shear divided by plasma viscosity (high values indicate low deformability)[10]; (*g*) leucocyte count (TOA cell counter); (*h*) total cholesterol (Boehringer assay); (*i*) serum triglyceride concentration (Merck assay); (*j*) erythrocyte sedimentation rate in the first hour (Westergren).

STATISTICAL ANALYSIS

We used the Kolmogoroff-Smirnov goodness of fit test to test all interval scaled data for normal distribution. Then we used three different statistical approaches: (*a*) the patient group was compared with the control group by the unpaired *t* test (p significant at $<0·05$); (*b*) the paired *t* test (p significant at $<0·05$) was applied to 20 pairs of patients and controls who were matched for cardiovascular risk profiles; (*c*) patients were grouped according to the interval since myocardial infarction (group A <2 years, group B 2–5, group C >5). For analysis of variance we used the Kruskal-Wallis test (software package SPSS/PC+ 3·0) (p values of $<0·05$ were regarded as significant).

Results

Comparison of matched pairs showed that standardised blood viscosity was significantly higher in patients at all shear rates. Plasma viscosity, haematocrit, and leucocyte count

Table 1 Data on patients and controls

	Patients (n (%))	*Controls (n (%))*
Male	45	17
Female	6	3
Age (yr):		
Mean (SD)	54·9 (5·0)	54·3 (6·0)
Range	(39–60)	(38–60)
Weight (kg):		
Mean (SD)	78·1 (9·3)	78·3 (10·6)
Range	(61·5–105)	(62–109)
Concomitant risk factors:		
Hypertension	23 (45)	15 (75)
Hyperlipidaemia	33 (65)	6 (30)
Currently smoking	4 (8)	5 (25)
Ex-smokers	37 (73)	11 (55)
Diabetes mellitus	14 (27)	5 (25)
Concomitant treatment:		
β blockers	18 (35)	3 (15)
Calcium antagonists	20 (39)	6 (30)
Diuretics	12 (24)	1 (5)
Nitrates	31 (61)	0 (0)
Aspirin	21 (41)	0 (0)
Fibrates	10 (2)	2 (10)
Uricosurics	9 (18)	1 (5)
ACE inhibitors	2 (4)	1 (5)
Digitalis	7 (14)	0 (0)

ACE, angiotensin converting enzyme.

were almost identical in matched pairs of patients and controls but red cell aggregation and erythrocyte sedimentation rate were nearly twice as high in patients. Red cell deformability was significantly reduced and blood lipid concentrations were similar in the two groups (table 2).

A comparison of the patient and control groups showed that the triglyceride concentration, erythrocyte sedimentation rate, and blood viscosity readings were significantly higher in the patients. All the other results were similar to those in the matched pairs comparison (table 2). The interval since acute myocardial infarction had no effect on any of the variables (table 3). Native blood viscosity tended to increase with time since infarction, while red cell aggregation and standardised blood viscosity (at lower shear rates) remained almost unchanged. Blood viscosity at high shear rates and red cell deformability tended to fall. Differences between subgroups were significant only when the control group was entered into the analysis.

Discussion

The plasma concentration of fibrinogen increases immediately after acute myocardial infarction.[11] This in turn increases plasma and blood viscosity[12] and red cell aggregation.[13] Reduced deformability of red and white cells has also been reported after the acute event.[14,15] We found that almost all these rheological changes persisted long after an acute myocardial infarction. Analysis of variance clearly showed that the rheological changes were not influenced by the interval since the acute event. Even in the long term there were no significant alterations in the rheological variables we studied.

One hypothesis is that the "rheological deficit" in such patients is not solely the consequence of the infarction but exists independently of it. Thus it might influence perfusion of the myocardium, particularly its microcirculation: normal blood is fluid when shear forces are high and viscous when they are low.[1] The changes in blood rheological variables that we detected must amplify this effect. Furthermore, vasoregulatory functions are impaired in the ischemic heart[16] so it may not be possible to increase flow to compensate for

Table 2 Rheological variables in patients and controls

	Matched pairs Patients (P) (n=20) v Controls (CO) (n=20)			*Groups: Total group (TG) (n=51) v Controls (CO) (n=20)*		
Variable	*Group*	*Mean (SD)*	*p*	*Group*	*Mean (SD)*	*p*
BV native at D = 94·5 s^{-1} (mPa s)	P	5·26 (0·54)		TG	5·38 (0·55)	< 0·05
	CO	5·10 (0·44)		CO	5·10 (0·44)	
BV native at D = 2·4 s^{-1} (mPa s)	P	17·62 (3·65)		TG	18·73 (3·76)	
	CO	17·45 (2·67)		CO	17·45 (2·67)	
BV native at D = 0·7 s^{-1} (mPa s)	P	32·34 (7·54)		TG	34·57 (8·10)	< 0·05
	CO	31·48 (5·46)		CO	31·48 (5·46)	
BV (HCT = 45%) at D = 94·5 s^{-1} (mPa s)	P	5·19 (0·32)	< 0·05	TG	5·18 (0·32)	< 0·01
	CO	4·88 (0·41)		CO	4·88 (0·41)	
BV (HCT = 45%) at D = 2·4 s^{-1} (mPa s)	P	17·08 (2·17)	< 0·05	TG	17·36 (2·05)	< 0·01
	CO	15·90 (1·83)		CO	15·90 (1·83)	
BV (HCT = 45%) at D = 0·7 s^{-1} (mPa s)	P	31·38 (5·49)	< 0·01	TG	31·62 (5·05)	< 0·01
	CO	28·07 (3·87)		CO	28·07 (3·87)	
RBC aggregation (units)	P	6·10 (2·19)	< 0·001	TG	6·79 (2·70)	< 0·001
	CO	3·88 (1·31)		CO	3·88 (1·31)	
RBC deformability (units)	P	4·24 (0·26)	< 0·001	TG	4·18 (0·26)	< 0·05
	CO	3·93 (0·33)		CO	3·93 (0·33)	
Haematocrit (%)	P	45·4 (3·86)		TG	46·1 (3·49)	
	CO	46·8 (3·09)		CO	46·8 (3·09)	
ESR (mm/1h)	P	8·65 (10·16)		TG	7·92 (7·55)	< 0·01
	CO	4·55 (3·66)		CO	4·55 (3·66)	
PV (mPa s)	P	1·23 (0·06)		TG	1·24 (0·06)	
	CO	1·25 (0·06)		CO	1·24 (0·06)	
Leucocytes (× 10^9/l)	P	6·20 (1·59)		TG	7·00 (2·27)	
	CO	6·78 (2·10)		CO	6·78 (2·10)	
Cholesterol (mmol/l)	P	6·10 (1·09)		TG	6·28 (1·09)	
	CO	6·08 (1·16)		CO	6·08 (1·16)	
Triglycerides (mmol/l)	P	1·89 (1·56)		TG	2·21 (1·89)	< 0·05
	CO	1·64 (0·66)		CO	1·64 (0·66)	

BV, blood viscosity; D, shear rate, HCT, haematocrit, PV, plasma viscosity, ESR, erythrocyte sedimentation rate, RBC, red blood cells.

Table 3 Rheology in relation to time after myocardial infarction

Variable	*Group*	*n*	*Mean (SD)*	*p1*	*p2*
BV native at D = 94·5 s^{-1} (mPa·s)	0–1 yr	10	5·31 (0·45)	0·870	0·093 (p $\leqslant$ 0·1)
	2–5 yr	19	5·42 (0·47)		
	> 5 yr	22	5·37 (0·66)		
	Controls	20	5·10 (0·44)		
BV native at D = 2·4 s^{-1} (mPa·s)	0–1 yr	10	18·0 (2·5)	0·801	0·395
	2–5 yr	19	18·7 (3·4)		
	> 5 yr	22	19·1 (4·5)		
	Controls	20	17·5 (2·7)		
BV native at D = 0·7 s^{-1} (mPa·s)	0–1 yr	10	32·1 (6·0)	0·580	0·296
	2–5 yr	19	34·8 (7·4)		
	> 5 yr	22	35·5 (9·5)		
	Controls	20	31·5 (5·5)		
BV (HCT = 45%) at D = 94·5 s^{-1} (mPa·s)	0–1 yr	10	5·26 (0·32)	0·084 (p $\leqslant$ 0·1)	0·002 (p $\leqslant$ 0·01)
	2–5 yr	19	5·27 (0·31)		
	> 5 yr	22	5·08 (0·30)		
	Controls	20	4·88 (0·41)		
BV (HCT = 45%) at D = 2·4 s^{-1} (mPa·s)	0–1 yr	10	17·6 (1·5)	0·387	0·031 (p $\leqslant$ 0·05)
	2–5 yr	19	17·7 (2·4)		
	> 5 yr	22	16·9 (1·9)		
	Controls	20	15·9 (1·8)		
BV (HCT = 45%) at D = 0·7 s^{-1} (mPa·s)	0–1 yr	10	31·3 (4·2)	0·663	0·050 (p $\leqslant$ 0·005)
	2–5 yr	19	32·6 (6·0)		
	> 5 yr	22	30·9 (4·5)		
	Controls	20	28·1 (3·9)		
RBC aggregation (units)	0–1 yr	10	6·78 (2·80)	0·863	0·000 (p $\leqslant$ 0·001)
	2–5 yr	19	6·87 (2·62)		
	> 5 yr	22	6·72 (2·85)		
	Controls	20	3·88 (1·31)		
RBC deformability (units)	0–1 yr	10	4·20 (0·29)	0·123	0·002 (p $\leqslant$ 0·01)
	2–5 yr	19	4·26 (0·22)		
	> 5 yr	22	4·10 (0·26)		
	Controls	20	3·93 (0·33)		

p1 = probability (Kruskal-Wallis ANOVA) that the means of three subgroups of patients with history of acute myocardial infarction (AMI dating back < 2 years, 2–5 years, > 5 years at time of measurements) do not differ from each other.
p2 = probability (Kruskal-Wallis ANOVA) that the means of all four subgroups (controls, AMI dating back < 2 years, 2–5 years, > 5 years at time of measurements) do not differ from each other.
See footnote to table 2 for abbreviations.

(local) hyperviscosity. This means that the flow properties of blood could be a significant determinant of blood flow in hypoperfused areas of the heart.

Evidence from other studies supports the above hypothesis. A rheological deficit similar to the one we found after acute myocardial infarction, was found in patients with coronary artery disease.[17] This deficit is related to the extent of the coronary atherosclerosis.[18] There are several reports of patients in whom angina was followed by infarction and the rheological abnormality was detected before the infarction took place.[19] The presence of rheological changes before and long after myocardial infarction implies that the abnormality cannot be solely the result of tissue necrosis and acute phase reactions.

Cardiovascular risk factors too are associated with discrete but significant rheological changes (for review see [20]). But they are unlikely to have contributed to the present results, because the results of the matched pairs study were the same as in the group analysis. Our data showed that the abnormality of blood rheology in patients with a history of myocardial infarction was independent of the acute event. The findings suggest that rheological mechanisms contribute to hypoperfusion in coronary artery disease.

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1 Chien S. Physiological and pathophysiological significance of hemorheology. In Chien S, Dormandy J, Ernst E, Matrai A, eds. *Clinical hemorheology*. Dordrecht: Martinus Nijhoff, 1987:125–64.

2 Most AS, Ruocco NA, Gewirtz H. Effect of a reduction in blood viscosity on maximal oxygen delivery distal to a moderate coronary stenosis. *Circulation* 1986;74:1085–92.

3 Dormandy J, Ernst E, Matrai A, Flute PT. Hemorheological changes following acute myocardial infarction. *Am Heart J* 1982;104:1364–7.

4 Dintenfass L. Viscosity factors in hypertensive and cardiovascular diseases. *Cardiovasc Med* 1977;2:337–54.

5 Dormandy JA. Cardiovascular diseases In: Chien S, Dormandy J, Ernst E, Matrai A, eds. *Clinical hemorheology*. Dordrecht Martinus Nijhoff, 1987:165–94.

6 Matrai A, Flute PT, Dormandy J. Improving accuracy of coaxial viscometry. *Biorheology* 1984;1·99–103.

7 Matrai A, Whittington RB, Ernst E. Correction of blood viscosities to standard hematocrit. *Clinical Hemorheology* 1987;7·261–5

8 Harkness J. The viscosity of human blood plasma; its measurement in health and disease. *Biorheology* 1971; 8·171–93.

9 Ernst E, Magyarosy I, Roloff Ch, Drexel H. A new simple method for measuring red cell aggregation. *Biorheology* 1984,1(suppl):217–9.

10 Chien S. Biophysical behaviour of red cells in suspensions. In. Surgenor P, ed. *The red blood cell, vol 2.* San Francisco: Academic Press, 1975:1031–132.

11 Jan K, Chien S, Bigger T. Observation on blood viscosity changes after acute myocardial infarction. *Circulation* 1975;51.1079–84.

12 Harkness J, Whittington RB. The viscosity of human blood plasma. Its changes in disease and on the exhibition of drugs. *Rheologica Acta* 1971;10:55–61.

13 Chien A Clinical rheology in cardiovascular disease. *Bibl Anat* 1976;16:172–83.

14 Dormandy J, Boyd M, Ernst E. Red cell filterability after myocardial infarction. *Scand J Clin Lab Invest* 1981; 41(suppl):156–8.

15 Juan-Vague J, Billerey M, Bonocore M. Decreased white blood cell filterability after myocardial infarction *Clinical Hemorheology* 1987;7:426–32.

16 Feigl EO. Coronary physiology. *Physiological Reviews* 1983,63:1–205.

17 Nicolaides AN, Bowers R, Horbourne T, Kinder PH, Besterman EM. Blood viscosity, red cell flexibility, haematocrit and plasma-fibrinogen in patients with angina *Lancet* 1977;ii 943–5.

18 Lowe GDO, Drummond MM, Lorimer AR. Relation between extent of coronary artery disease and blood viscosity. *Br Med J* 1980,i:613–4.

19 Volger E. Bedeutung der Fließeigenschaften des Blutes bei drohendem Myokardinfarkt. *Hämostaseologie* 1986; 6.118–23.

20 Lowe GDO. Hemorheology and blood diseases. In: Chien S, Dormandy J, Ernst E, Matrai A, eds. *Clinical hemorheology*. Dordrecht· Martinus Nijhoff, 1987·227–54.

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Prospective evaluation of a protocol for induction of sustained ventricular tachycardia in patients referred to a tertiary centre

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Abstract

All eight stages of a stimulation protocol that used one then two extrastimuli from the right ventricular apex in sinus rhythm and three ventricular drive rates (100, 120, and 140 beats/min) were performed in 24 patients with recurrent spontaneous sustained ventricular tachycardia despite drug treatment. Twenty two of the patients had sustained a previous myocardial infarct and 18 were on long term treatment with amiodarone. Sustained (>30 s) ventricular tachycardia was induced in all patients. Two extrastimuli were significantly more likely to induce sustained ventricular tachycardia than one extrastimulus, both overall and individually for the three ventricular drive rates. A ventricular drive rate of 140 beats/min was significantly more likely to induce ventricular tachycardia than ventricular drive rates of 100 and 120 beats/min which were significantly more effective than sinus rhythm. A ventricular drive rate of 140 beats/min with one or two extrastimuli induced ventricular tachycardia in 23/24 (95%) of the patients in this study.

The full eight stage protocol was progressive separately for both extrastimuli and ventricular drive rate but the last two stages (ventricular drive rate of 140 beats/min with one or two extrastimuli) were as effective as the entire protocol in inducing ventricular tachycardia.

Programmed ventricular stimulation is performed in patients with recurrent sustained ventricular tachycardia either as part of serial drug studies to identify suppressive treatment or to localise the origin by activation mapping.[1-4] Most protocols are performed as a fixed series of steps in the belief that each successive stage both adds to the overall sensitivity and individually is more likely to induce tachycardia than the previous step. Although different stimulation protocols have been assessed as a whole for their ability to initiate tachycardia, the relative likelihood that individual stages of the protocol will induce ventricular tachycardia has not been evaluated. Consequently, it is not known whether the steps in a stimulation protocol are, individually, increasingly likely to induce tachycardia or are a random sequence of equally effective steps.[5,6]

To evaluate the relative sensitivity and specificity of individual steps within a stimulation protocol, we performed all eight stages, irrespective of whether sustained ventricular tachycardia was induced at any stage.

Patients and methods

The study was performed prospectively in consecutive patients undergoing programmed ventricular stimulation as a baseline for serial drug testing to design appropriate treatment. Patients gave their written informed consent before they entered the study. All antiarrhythmic drugs (except amiodarone) were stopped for at least five half lives before the study. The patient was starved for at least four hours before the study and no premedication was given. All patients had previously undergone cardiac catheterisation to exclude critical coronary artery disease.

Patients were included if the induced ventricular tachycardia was sustained, haemodynamically stable, and could be terminated by programmed stimulation. Patients with haemodynamically unstable ventricular tachycardia, associated severe angina, or uncontrolled left ventricular failure were excluded. Ventricular tachycardia was defined as non-sustained if there were six or more beats of tachycardia with spontaneous termination within 30 seconds and sustained if the tachycardia lasted more than 30 seconds. Patients whose tachycardia required intervention to terminate their arrhythmia before 30 seconds were not included in this study. The tachycardia was described as "uniform" if no change was seen in the configuration of tachycardia and "clinical" if it was identical in configuration to a 12 lead electrocardiogram of spontaneous tachycardia. The electrophysiological diagnosis was established by conventional criteria with His and atrial electrograms.[7]

The programmed stimulation protocol was based on that described by Zehender *et al* and Brugada and Wellens[5,6] and used an electrode in the right ventricular apex. The stimulation pulse was a 2 ms square wave with an amplitude of twice the diastolic threshold. The stimulation procedure was recorded with an eight channel Siemens-Elema Mingograf chart recorder. A standard 12 lead electrocardiogram was always recorded in sinus rhythm and if tachycardia was initiated. One and then two extrastimuli were introduced during sinus rhythm and after three ventricular drives of eight beats at 100, 120, and 140 beats per

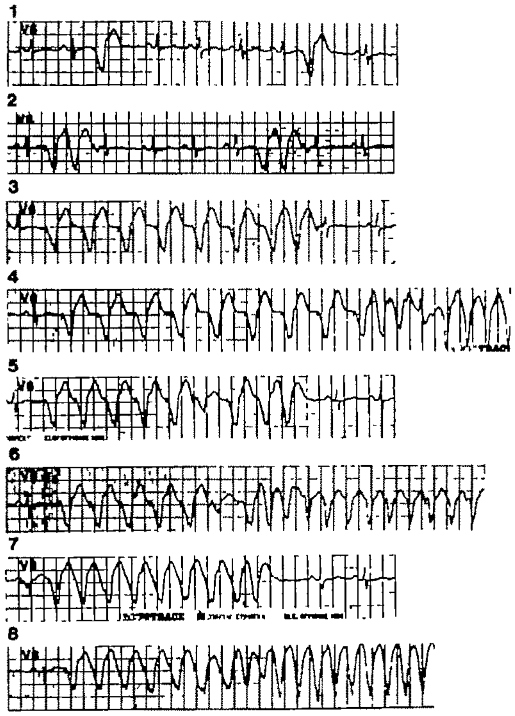

Figure 1 First eight stages of the protocol recorded in V6 at a paper speed of 25 mm/s. Stages one, three, five, and seven were one extrastimulus in sinus rhythm and after ventricular drive rates of 100, 120, and 140 beats/min. Stages two, four, six, and eight were two extrastimuli in sinus rhythm and after the three ventricular drive rates. In this patient (case 21) sustained ventricular tachycardia was induced in stages four, six, and eight. It had the same configuration in all 12 leads, but the tachycardia induced at stage eight was faster (RR = 280 ms compared with 330 ms at stages four and six).

minute (fig 1). The extrastimulus was introduced in late diastole (20 ms less than the pacing cycle length) and its coupling interval to the last driven beat was then reduced by 20 ms decrements until the effective refractory period was reached. The effective refractory period was established more precisely by 10 ms decrements. The first extrastimulus coupling interval was then increased to 20 ms beyond the effective refractory period and the second extrastimulus was introduced in late diastole (20 ms less than the ventricular drive cycle length) and again reduced by 20 ms decrements. If sustained ventricular tachycardia was induced it was terminated electively after 30 seconds with conventional pacing techniques. When tachycardia was induced, the next stage of the protocol was performed after a three minute pause to allow the sinus rate to return to baseline. If sustained tachycardia was induced only after three extrastimuli, the protoçol was terminated and the patient was not included in this study because of the concern that three extrastimuli might provoke ventricular fibrillation.[8-13]

ANALYSIS

We used Student's paired *t* test to compare the rates of tachycardia induced at each stage and McNemar's test for matched samples with Yates's continuity correction to compare the relative proportions of patients in whom ventricular tachycardia was induced at each stage.

Results

A total of 41 patients was considered for the study. Non-sustained tachycardia only was induced in eight patients, three patients were haemodynamically unstable during tachycardia, one patient had a significant stenosis of the left main coronary artery, sustained tachycardia was inducible only with burst pacing or three extrastimuli in three patients, and no tachycardia was induced in two patients. Twenty four patients entered the study with inducible sustained ventricular tachycardia. Three of these patients also had non-sustained tachycardia induced at an earlier stage of the protocol. All 24 patients had presented with sustained ventricular tachycardia. The table shows the details of individual patients. Most (22/24) of patients had ischaemic heart disease (all had suffered a myocardial infarction more than one month before), two patients had congestive cardiomyopathy, and 18 of the patients were receiving long term treatment with amiodarone. The table shows the results of the programmed stimulation for each patient. In two patients non-clinical stable uniform ventricular tachycardia only was induced. No multiform or haemodynamically unstable ventricular tachycardia or ventricular

Results of each stage of the stimulation protocol in each patient

Patient No.	*Age*	*Sex*	*Disease*	*Stage* 1	2	3	4	5	6	7	8
1	63	M	NH						NS		S
2	62	M	IHD				S		S		S
3	75	F	IHD				S		S		S
4	63	M	IHD	S				S		S	
5	65	M	IHD				S		S		S
6	59	M	IHD		S		S	S	S	S	S
7	56	M	IHD				S		S	S	S
8	56	M	IHD		S		S	S	S	S	S
9	66	M	IHD						S		S
10	52	M	IHD							S	
11	57	M	IHD				S	S	S	S	S
12	57	M	IHD	S			S		S	S	S
13	58	F	IHD				S				S
14	49	M	IHD				S		S		S
15	62	M	IHD				S				S
16	57	M	IHD				NS				S
17	64	M	IHD								S
18	64	M	IHD						NS		S
19	67	M	IHD		S		S	S	S	S	S
20	77	F	IHD						S		
21	57	M	IHD		S		S		S		S
22	47	M	NH						S		S
23	68	M	IHD								S
24	51	M	IHD					S	S		S

IHD, ischaemic heart disease, NH, normal heart, NS, non-sustained ventricular tachycardia; S, sustained ventricular tachycardia.

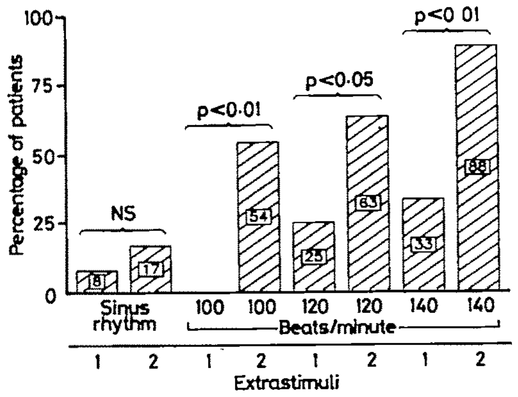

Figure 2 Ventricular tachycardia induced at each stage in the 24 patients in whom tachycardia was sustained, expressed as a percentage of the total. P was calculated by McNemar's test for matched pairs with Yates's correction.

fibrillation was induced after stable ventricular tachycardia had been induced at a previous stage in any patient. In the patients where ventricular tachycardia was induced at more than one stage the RR interval of ventricular tachycardia induced at the later stage (mean (SD) 357 (89) ms) was not significantly shorter (paired t test) than that of the ventricular tachycardia induced at the earlier stage (mean 375 (98) ms).

Figure 2 shows the proportion of patients in whom sustained ventricular tachycardia was induced at each stage. Double extrastimuli and faster ventricular drive rates increased the proportion of patients in whom ventricular tachycardia was induced. The difference between one and two extrastimuli was significant ($p < 0.01$) overall and individually for the three ventricular drive rates but only approached significance in sinus rhythm. Extrastimuli in sinus rhythm induced ventricular tachycardia in a much lower proportion of patients than any of the other stages except one extrastimulus with a ventricular drive rate of 100 beats/min (fig 2). In ascending order of effectiveness the sequence was stages 3, 1, 2, 5, 7, 4, 6, 8. Figure 3 shows that the likelihood of inducing ventricular tachycardia was progressively greater for both an increasing number of extrastimuli and for faster ventricular drive rates. At a ventricular drive rate of 140 beats/min one or two extrastimuli were significantly more effective at inducing ventricular tachycardia than during either sinus rhythm or after ventricular drive rates of 100 or 120 beats/min ($p < 0.05$). At all the ventricular drive rates extrastimuli were significantly more likely to induce ventricular tachycardia than during sinus rhythm ($p < 0.05$). The difference between ventricular drive rates of 100 beats/min and 120 beats/min was not significant.

In only one patient (case 20) was ventricular tachycardia not induced with one or two extrastimuli delivered after a ventricular drive rate of 140 beats/min when ventricular tachycardia had been induced at an earlier stage. Ventricular tachycardia was induced by one extrastimulus but not by two extrastimuli in two patients and only by two extrastimuli in 15 patients.

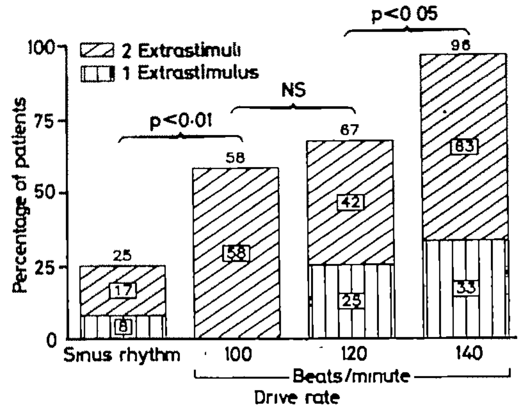

Figure 3 Cumulative total of induced ventricular tachycardia during sinus rhythm and during each ventricular drive rate for the 24 patients with sustained ventricular tachycardia for one and then two extrastimuli. P was calculated by McNemar's test for matched pairs with Yates's correction.

Discussion

This study examined the sensitivity and specificity of individual steps in relation to the other steps in an eight stage protocol. The patients had been referred for electrophysiologically guided treatment of recurrent, drug resistant ventricular tachycardia. In this population the purpose of programmed ventricular stimulation was the induction of sustained ventricular tachycardia, either as part of serial drug testing or to allow activation mapping of the origin(s) of the tachycardia.

Complete suppression of inducibility of ventricular tachycardia has a positive predictive value of 90–95% for an arrhythmia free clinical course,[1] but continued inducibility has a lower negative predictive value, with recurrent arrhythmias occurring in 40–85% of patients.[1,2] Complete suppression is relatively rate[1,2] but there is evidence that if induction of tachycardia is made more difficult by drug treatment then this also predicts a good clinical response to that drug.[3,4] To assess accurately the ease or difficulty of induction, the relative ability of the individual steps in a protocol to induce tachycardia must be known.

Other studies showed that use of one or two extrastimuli from the right ventricle apex in sinus rhythm after three ascending ventricular drive rates of 100, 120, and 140 beats/min gave a cumulative increase in the proportion of patients in whom ventricular tachycardia could be induced.[5,6] In these studies the data were cumulative, with the induction of clinical ventricular tachycardia as the end point and the independent contribution of each stage was not assessed. When the percentage of patients who had ventricular tachycardia induced at each stage was calculated, a similar pattern was observed to that seen in this study; though stage 6 (120 beats/min and two extrastimuli) was more successful at inducing ventricular tachycardia than stage 8 (140 beats/min and two extrastimuli).[5] The major difficulty in interpreting their data was that the later stages were performed only on a subset of the population because those patients who had had ventricular tachycardia induced at an earlier stage were excluded. In contrast, in our study all eight stages were performed in each patient and we showed that stage eight alone was more effective in inducing ventricular tachycardia than stages four or six, which in turn were more effective than stage two. Our data also showed that two extrastimuli were more likely to initiate ventricular tachycardia than was a single extrastimulus. Where both non-sustained and sustained ventricular tachycardia were induced in an individual, the sustained ventricular tachycardia was always induced when a faster ventricular drive rate was used.

On the basis of these results it would be logical to rearrange the order to produce a graded protocol. The initial steps would be a single extrastimulus in sinus rhythm and after drive rates of increasing rate, followed by double extrastimuli. This would represent a more truly progressive protocol than the original protocol because two extrastimuli after a drive rate of 100 beats/min were a more vigorous test than one extrastimulus after a drive rate of 140 beats/min. The drive rate of 120 beats/min could be omitted because this was not significantly different from 100 or 140 beats/min (supported by the study by Borggrefe *et al*[4]).

This study showed that the two stages, one or two extrastimuli with a ventricular drive of 140 beats/min, were nearly as sensitive (95%) as the eight stage protocol in our group of patients. Therefore, it seems logical to perform only these two stages if inducibility of tachycardia was the only end point (that is, for activation mapping).

The patient population was not prospectively selected but was obviously biased by referral by other centres of patients with drug resistant, sustained ventricular tachycardia. This patient group closely reflects that seen in our clinical practice. Most (22/24) patients had had a previous myocardial infarction and many (18/24) were taking amiodarone. This limits the generalisation of the results to other groups of patients, though centres that perform programmed stimulation are likely to experience a similar referral pattern. Our results are consistent with those reported in patients with ischaemic heart disease not taking amiodarone.[4 8 9] The mechanism of tachycardia in our patient population was reentry in the myocardium due to localised slow conduction, the basis of nearly all sustained uniform ventricular tachycardia.[7] The results are not applicable to patients with right ventricular outflow tract tachycardia (due probably to triggered automaticity) which may be more easily induced with slower drive rates or the addition of isoprenaline.[10]

The design of this study was constrained by ethical considerations. Published reports support graded stimulation in serial drug testing[3 4]; therefore it was important to identify the weakest stimulation stage that induced tachycardia if the stimulation protocol was being performed as part of serial drug testing. If a random order of stimulation had been followed in this protocol then all stages would have to be performed, which may have necessitated multiple DC cardioversion in patients who would otherwise have been excluded (because of haemodynamically unstable tachycardia). The results may therefore reflect a sequence effect. However, they do not show a simple sequence because single extrastimuli induced significantly less ventricular tachycardia than double extrastimuli. There was also a pause after termination of each ventricular tachycardia before we went on to the next stage. Three extrastimuli were not included in the trial because of the associated high risk of non-clinical multiform ventricular tachycardia or ventricular fibrillation.[8 9 11–14].

This study examined the relative (not absolute) sensitivity and specificity of the individual steps within this protocol, which were close to the consensus,[15] and did not explore other controversies in programmed stimulation. The use of multiple sites in the right and left ventricle is probably not practical in serial drug studies. In screening procedures the use of a third extrastimulus or a faster drive rate were shown to be as sensitive as using the right ventricular outflow tract[6 12 16] or left ventricular pacing sites.[17] Increasing the strength of the current to decrease the refractory period does not seem to increase sensitivity but may decrease specificity.[6 12 18]

Different stages of the protocol did not induce different configurations of ventricular tachycardia. This was probably a direct result of limiting the number of extrastimuli to two in patients with systained ventricular tachycardia. This suggests that if a non-clinical ventricular tachycardia is induced initially, increasing the ventricular drive rate or number of extrastimuli (up to a maximum of two) is unlikely to induce the clinical tachycardia; two patients in this trial had only non-clinical tachycardia induced. Ventricular fibrillation or haemodynamically unstable ventricular tachycardia were not induced at a later stage if stable ventricular tachycardia had been induced initially in any patient. This suggests that while the later stages of this protocol were more likely to induce ventricular tachycardia, they were not more likely to induce ventricular fibrillation or a very rapid ventricular tachycardia. The rate of ventricular tachycardia induced at a later stage was not significantly faster than the tachycardia induced at an earlier stage. Thus if only a ventricular drive rate of 140 beats/min and one or two ventricular extrasystoles were used to induce ventricular tachycardia for mapping or screening purposes it would be no more likely to provoke a faster or more unstable tachycardia than would result from running through the full protocol.

This study and earlier reports support the concept that an increase in the number of extrastimuli and an increase in the drive rate independently increase the likelihood of the induction of ventricular tachycardia. We recommend that when programmed electrical stimulation is used to assess drug treatment a single extrastimulus should be introduced during sinus rhythm and then after two ventricular drive rates at 100 beats/min and 140 beats/min. Double extrastimuli should then be introduced during sinus rhythm and after this the two ventricular drive rates may be added, producing a six stage protocol. If the aim of the study is only to induce tachycardia (for mapping) then the protocol should start with one and two extrastimuli after a ventricular drive at 140 beats/min. This study suggests that this two stage protocol has nearly the same sensitivity (in the population studied) as the full eight stage protocol. If these two steps fail to induce tachycardia then three extrastimuli or pacing at a different site may be necessary to balance the increase in sensitivity with the decrease in specificity.

1 Ruskin JN, Schoenfeld MH, Garan H. Role of electrophysiologic techniques in the selection of antiarrhythmic drug regimens for ventricular arrhythmias. *Am J Cardiol* 1983,52 41C–6C.

2 Swerdlow CD, Blum J, Winkle RA, Griffin JC, Ross DL, Mason JW Decreased incidence of antiarrhythmic drug efficacy at electrophysiologic study associated with the use of a third extrastimulus *Am Heart J* 1982,104:1004–11.

3 Borggrefe M, Trampisch H, Breithardt G Re-appraisal of criteria for assessing drug efficacy in patients with ventricular tachyarrhythmias complete versus partial suppression of inducible arrhythmias *J Am Coll Cardiol* 1988,12.140–9.

4 DiMarco J, Garan H, Ruskin J Partial suppression of induced arrhythmias during serial electrophysiologic testing [Abstract]. *Circulation* 1980;63(suppl II) 261

5 Zehender M, Brugada P, Geibel A, Waldecker B, Stevenson W, Wellens HJ Programmed electrical stimulation in healed myocardial infarction using a standardized ventricular stimulation protocol *Am J Cardiol* 1987,59 578–85

6 Brugada P, Wellens HJ Comparison in the same patient of two programmed ventricular stimulation protocols to induce ventricular tachycardia. *Am J Cardiol* 1985,55. 380–3.

7 Ward DE, Camm AJ *Clinical electrophysiology of the heart* London: Edward Arnold, 1987 9–31

8 Brugada P, Green M, Abdollah H, Wellens HJ Significance of ventricular arrhythmias initiated by programmed ventricular stimulation. the importance of the type of ventricular arrhythmia induced and the number of extrastimuli required. *Circulation* 1984,69 87–92.

9 Brugada P, Abdollah H, Heddle B, Wellens HJ. Results of a ventricular stimulation protocol using a maximum of 4 premature stimuli in patients without documented or suspected ventricular arrhythmias *Am J Cardiol* 1983; 52:1214–8.

10 Lerman BB, Belardinelli L, West A, Berne RM, DiMarco JP. Adenosine sensitive ventricular tachycardia evidence suggesting cyclic AMP mediated triggered activity *Circulation* 1986,74 270–80

11 Morady F, Shapiro W, Shen E, Sung RJ, Scheinman MM. Programmed ventricular stimulation in patients without spontaneous ventricular tachycardia. *Am Heart J* 1984,107·875–82.

12 Herre JM, Mann DE, Luck JC Effect of increased current, multiple pacing sites and number of extrastimuli on induction of ventricular tachycardia *Am J Cardiol* 1986, 57 102–7

13 Wellens HJ, Brugada P, Stevenson WG. Programmed electrical stimulation of the heart in patients with life threatening arrhythmias what is the significance of induced arrhythmias and what is the correct stimulation protocol. *Circulation* 1985;72 1–7

14 Buxton AE, Waxman HL, Marchlinski FE, Untereker WJ, Waspe LE, Josephson ME. Role of triple extrastimuli during electrophysiologic study of patients with documented sustained ventricular tachycardia *Circulation* 1984, 69·532–40

15 Ward DE. Can the technicalities of electrophysiological testing for ventricular tachycardia be simplified? *Br Heart J* 1987,58 437–40

16 Kudenchuk J, Kron J, Walance C, McAnulty J The limited value of programmed electrical stimulation from two right ventricular sites in patients with clinical sustained ventricular tachyarrhythmias [Abstract] *PACE* 1987,10·448

17 Lin H, Mann DE, Luck JC, *et al* Prospective comparison of right and left ventricular stimulation for induction of sustained ventricular tachycardia *Am J Cardiol* 1987;59.559–63

18 Weissberg PL, Broughton A, Harper RW, Young A, Pitt B Induction of ventricular arrhythmias by programmed ventricular stimulation a prospective study on the effects of stimulation current on arrhythmia induction *Br Heart J* 1987,58·489–94

Br Heart J 1990;64:256–60

Placebo controlled trial of xamoterol versus digoxin in chronic atrial fibrillation

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Abstract

Thirteen patients in chronic atrial fibrillation with a normal resting heart rate but with exercise tachycardia and episodes of bradycardia were randomised to treatment periods of two weeks on xamoterol (200 mg twice daily), low dose digoxin, or placebo, in a blind crossover study. The results (mean SEM) of symptom scores, a treadmill exercise test, and 24 hour ambulatory electrocardiographic monitoring were obtained. Xamoterol improved symptom scores and controlled exercise heart rate better than digoxin. Xamoterol was better than digoxin or placebo in reducing the heart rate response to exercise and tended to improve exercise duration. Xamoterol, by reducing the daytime maximum hourly heart rate and increasing the night time minimum hourly heart rate, significantly reduced the difference between the two compared with placebo. In contrast, digoxin tended to reduce both the maximum and minimum hourly heart rates through day and night. Both the frequency and duration of ventricular pauses were reduced by xamoterol but tended to increase with digoxin.

Xamoterol reduced both the circadian variation in ventricular response to atrial fibrillation and exercise tachycardia by modulating the heart rate according to the prevailing level of sympathetic activity. These changes were translated into symptomatic benefit for the patients studied.

Medical treatment of chronic atrial fibrillation has largely concentrated on the control of tachycardia. However, recent 24 hour ambulatory electrocardiographic studies emphasised the wide circadian variation in heart rate in chronic atrial fibrillation,[1] and the importance of episodic ventricular standstill.[2] Tachycardia of more than 140 beats/min associated with bradycardia of less than 50/min and nocturnal pauses of up to 4·0 s are commonly found in patients thought to be optimally treated.[1] In fact, digoxin, the most widely used treatment, tends to provoke or aggravate bradycardia by its vagomimetic effect.[3]

Xamoterol is a selective β_1 adrenoceptor partial agonist that has 43% of the stimulant activity of the full agonist isoprenaline.[4] At low levels of sympathetic activity, it occupies the β_1 receptors to produce both positive inotropic and chronotropic effects on the heart.[5] When sympathetic activity increases, it behaves as a competitive antagonist at the β_1 receptor.[6] This ability of xamoterol to stabilise activation of the β_1 receptor may be of use in modulating the ventricular response to atrial fibrillation in patients whose heart rate shows considerable circadian variation. We investigated the effects of xamoterol, digoxin, and placebo on symptoms, exercise performance, and 24 hour control of heart rate in patients with chronic atrial fibrillation and normal resting heart rate who showed exercise tachycardia during the day and episodes of bradycardia, especially at night.

Patients and methods

PATIENTS

We studied 13 patients (seven women) aged 55–84 years (mean 67). All had chronic atrial fibrillation and electrocardiographic evidence of bradycardia at rest that had caused the attending physician to reduce or stop specific treatment. Patients had a documented resting heart rate of < 50 beats/min before the dose of digoxin was reduced. All patients had at least one ventricular pause of 1·5 s after digoxin was stopped. Ten patients had conduction abnormalities on the electrocardiogram: three had bifascicular block, two had right bundle branch block, two had right axis deviation, and three had non-specific intraventricular conduction defects. No patient complained of syncope but ten patients reported dizziness and six palpitation. All patients experienced some degree of breathlessness or fatigue on exertion. Eight were in the New York Heart Association class I category, and five in class II (who needed diuretics). The aetiology was non-rheumatic valvar heart disease in four patients; rheumatic valvar heart disease in three; two were "lone" fibrillators; and there was one case each of ischaemic heart disease, constrictive pericarditis, post-thyroidectomy, and hypertrophic cardiomyopathy. Six patients took no specific treatment for atrial fibrillation, six were taking digoxin 0·125 mg daily (5) or 0·0625 mg daily (1); one patient was taking atenolol 50 mg daily. Other important medications were frusemide, warfarin, thyroxine, captopril, and bendrofluazide. We obtained informed consent from each patient after a full explanation of the study.

DESIGN

Treatment with digoxin and atenolol was

stopped in the six patients who were taking it; these patients were then observed and assessed for at least two weeks before entry into the study. Each patient underwent three treatment periods—one each of xamoterol, digoxin, and placebo—in a randomised cross-over fashion. Each treatment period lasted two weeks and was followed by a two week wash out period before the next treatment. Xamoterol (200 mg) and its matching placebo were given twice daily. Digoxin tablets were started at 0·5 mg on the first day of the treatment period, then the maintenance dosage was adjusted from 0·0625 mg daily to achieve a low therapeutic serum concentration.

The treatments were administered by an investigator who was not involved in the assessment. The other investigators and technicians conducting the investigations were not aware of the current treatment phase. Patients were assessed at entry into the study and reassessed at the end of each treatment period. The assessment comprised symptomatic evaluation, a treadmill exercise stress test, and 24 hour ambulatory electrocardiographic monitoring. Dizziness, palpitation, and breathlessness were rated for frequency on a descriptive 5 point scale. We assessed heart rate variability with 24 hour ambulatory electrocardiography on Reynolds Tracker recorders and analysis by a visually assisted Reynolds Pathfinder 3 system. We measured the maximum and minimum hourly heart rates, the number of ventricular pauses $> 1·5$ s, and the longest ventricular pause in 24 hours. (The heart rate was calculated from 15 s electrocardiographic strips.) A symptom limited treadmill exercise test was performed according to the modified Bruce protocol. The resting heart rate before the exercise was measured after the patient had sat down for five minutes. During the exercise, heart rate was monitored continuously and blood pressure was measured every minute. The maximum heart rate, maximum blood pressure, and exercise duration were recorded.

STATISTICAL ANALYSIS

To assess the differential effect of xamoterol on the circadian control of heart rate, the 24 hour data on heart rate were analysed over two 12 hour periods: 10 am to 9 pm (day) and 10 pm to 9 am (night). The area under the curve (AUC) of the plot of heart rate against time, calculated by the trapezoidal rule, reflects the mean heart rate over the time measured. For the day period, each area under curve of the maximum and minimum heart rates, termed AUC (day max) and AUC (day min) respectively, was calculated. AUC (night max) and AUC (night min) were similarly derived for the night period. The overall difference between the three treatment groups was determined by two way analysis of variance for the heart rate and exercise data, after we had checked for normality and equality of variance. If the variance ratio obtained was significant at the 5% level, we performed multiple paired comparisons between treatment groups using contrasts. Symptom scores and the number of ventricular pauses in 24 hours were analysed by Friedman two way analysis of variance by ranks. When the Friedman analysis showed a significant treatment effect, individual paired comparisons were carried out by the critical range method.[7] Results are given as mean (SEM). The 95% confidence intervals (95% CI) were calculated where appropriate. A p value of $< 0·05$ was regarded as significant.

Table 1 Comparative data on scores for symptom frequency (mean (interquartile range))

Symptom	*Placebo*	*Xamoterol*	*Digoxin*
Palpitation	2·0 (1·0–3·0)	1·5 (1·0–1·8)	1·8 (1·0–2·8)
Dizziness	1·6 (1·0–1·7)	1·2 (1·0–1·3)	1·7 (1·0–2·3)
Breathlessness	2·6 (1·3–3·8)	2·2 (1·3–3·0)	2·7 (2·0–3·8)

Results

Statistical analysis was carried out on the results from 12 patients who completed all phases of the study. In one patient, a 58 year old woman with valvar heart disease and symptoms (New York Heart Association class II), nausea, vomiting, and increased dyspnoea developed with two days of the start of xamoterol treatment. When xamoterol was stopped she improved but continued to feel unwell. Further investigations did not show an organic cause. During the digoxin treatment phase, five patients were given digoxin 0·0625 mg daily, the other seven patients were given 0·125 mg daily, and a mean serum concentration of 0·7 (0·1) nmol/l was achieved at completion of the treatment phase, when assessment took place. Analysis for possible period effect based on the exercise test results showed no significant differences between the three treatment periods.

SYMPTOM SCORES

Table 1 shows the comparative data on symptom scores based on a descriptive 5 point frequency scale. The symptom scores for the three treatments for palpitation, dizziness, and breathlessness were similar, although the scores for xamoterol seemed to be consistently lower than those for digoxin or placebo. Digoxin tended to produce less palpitation than placebo but more dizziness and breathlessness. Although there were no significant differences between individual symptoms during any treatment phase, a combined symptom score showed that patients had significantly more symptoms on digoxin than on xamoterol ($p < 0·05$).

EXERCISE TEST

Table 2 shows the comparative data on exercise test for the three treatments. The resting heart rate before the exercise test was significantly lower with digoxin treatment than with xamoterol ($p < 0·005$) or placebo ($p < 0·01$). There was no significant difference between xamoterol and placebo. The maximum heart rate on exercise was significantly lower with xamoterol treatment than with placebo or

Table 2 Comparative data obtained from exercise test (mean (SEM))

	Placebo (Pl)		p (Pl v X)	Xamoterol (X)		p (X v D)	Digoxin (D)		p (D v Pl)
Resting HR (beats/min)	70	(5)	NS	72	(5)	<0·005	62	(5)	<0·01
Peak HR (beats/min)	159	(12)	<0·001	136	(10)	<0·005	150	(10)	NS
Peak SAP (mm Hg)	181	(10)	NS	174	(8)	NS	170	(9)	NS
Peak DAP (mm Hg)	83	(3)	NS	87	(4)	NS	84	(2)	NS
PR product (mm Hg × min)	28612	(2545)	<0·001	23668	(2110)	NS	25786	(2412)	<0·05
Exercise duration (min)	9·7	(1·1)	NS	10·7	(0·9)	NS	10·2	(1·0)	NS

HR, heart rate, SAP, systolic arterial pressure, DAP, diastolic arterial pressure, PR, pressure × rate.

digoxin; the values for placebo and digoxin were not significantly different from each other (p = 0·45). There were no significant differences between the three treatments in the peak exercise systolic or diastolic blood pressure. The maximum pressure-rate product was significantly reduced by xamoterol and digoxin compared with placebo; but there was no significant difference between the two active treatments (p = 0·17). The patients tended to exercise longer on xamoterol treatment (95% CI: 10·0–11·4 min) than placebo (95% CI: 9·0–10·4 min) or digoxin (95% CI: 9·5–10·9 min), though this difference did not achieve statistical significance (p = 0·20).

HOURLY HEART RATE DATA

Figure 1A shows the effects of the three treatments on the maximum hourly heart rate over a 24 hour period, and fig 1B similarly shows the minimum hourly heart rate. Figure 2A shows the area-under-curve analysis of the data on maximum and minimum hourly heart rate from 10 am to 9 pm (day), and figure 2B the data from 10 pm to 9 am (night). Compared with placebo, xamoterol tended to reduce both AUC (day max) and AUC (day min) but increase both AUC (night max) and AUC (night min). Digoxin, in contrast, tended to reduce the values of all four variables compared with placebo or xamoterol. The difference between the areas under the curves of the plots of maximum and minimum hourly heart rate reflects the variability of the heart rate within the hour. Table 3 shows that the heart rate variability within the hour was similar in the three treatment groups. However, the circadian variability as indicated by AUC (day max)–AUC (night min) was significantly lower with xamoterol treatment than with either digoxin (p < 0·05) or placebo (p < 0·01). Compared with placebo, xamoterol increased the lowest minimum hourly heart rate from 50 (4) beats/min to 59 (5) beats/min (p < 0·05) but reduced the highest maximum hourly heart rate from 139 (8) beats/min to 132 (8) beats/min (p = 0·30) (table 4). Digoxin produced lower values for both the variables (45 (3) and 131 (8) beats/min respectively) than either xamoterol or placebo; the lowest minimum hourly heart rate was significantly different from the xamoterol value (p < 0·001).

VENTRICULAR PAUSES

Table 4 shows that xamoterol reduced the number of ventricular pauses (>1·5 s) in 24 hours compared with placebo or digoxin; the comparison with digoxin was significant (p < 0·05). The pauses were most frequent between 1 am and 6 am and least common between 1 pm and 6 pm. The maximum ventricular pause in 24 hours was the longest with digoxin treatment (95% CI: 2·2 to 2·8 s),

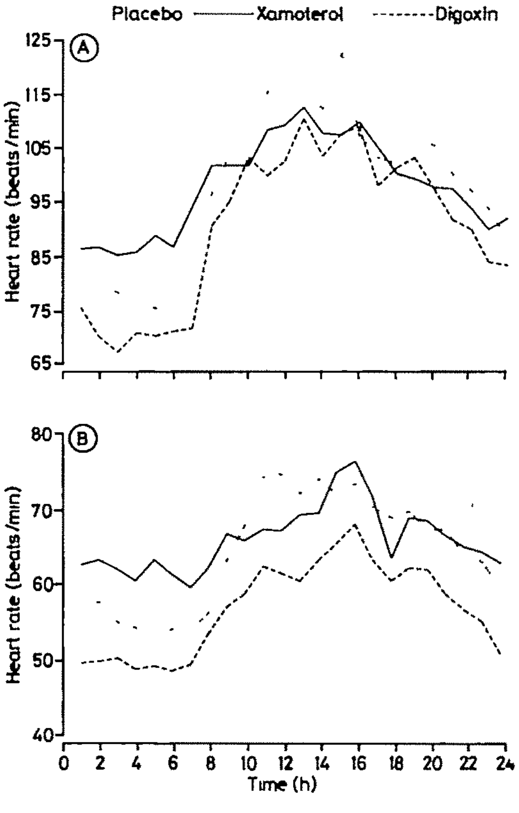

Figure 1 (A) Maximum hourly heart rate over a 24 hour period. (B) Minimum hourly heart rate over a 24 hour period.

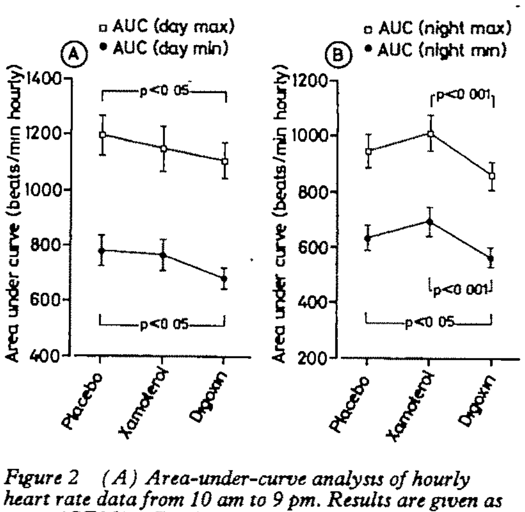

Figure 2 (A) Area-under-curve analysis of hourly heart rate data from 10 am to 9 pm. Results are given as mean (SEM). (B) Area-under-curve analysis of hourly heart rate data from 10 pm to 9 am

Table 3 Comparative data on variability of heart rate by area-under-curve analysis (mean (SEM))

	Placebo	*Xamoterol*	*Digoxin*
AUC (day max)—AUC (day min) (beats/min hourly)	417 (27)	386 (37)	427 (32)
AUC (night max)—AUC (night min) (beats/min hourly)	312 (18)	319 (39)	296 (22)
AUC (day max)—AUC (night min) (beats/min hourly)	565 (39)	458* (47)	546 (35)

*Xamoterol *v* placebo, p <0·01; xamoterol *v* digoxin, p <0·04

unaltered by placebo (95% CI: 2·0 to 2·6 s), but reduced significantly by xamoterol (95% CI: 1·5 to 2·1 s).

Discussion

In a placebo controlled study of patients with chronic atrial fibrillation characterised by normal resting heart rate, but with both exercise induced tachycardia and episodes of bradycardia, xamoterol seemed to be better than digoxin. Xamoterol treatment was more effective than digoxin in reducing exercise tachycardia and was accompanied by an improvement in exercise duration. Compared with digoxin, xamoterol reduced the frequency and duration of ventricular pauses and restored the minimum hourly heart rates to the normal range (fig 1B).

An important limitation in our selection of patients was that ethical considerations prevented us from recruiting patients with obvious symptomatic bradycardia or from placing them on conventional doses of digoxin. Only a few studies of the medical treatment of chronic atrial fibrillation have addressed the problem of bradycardia.[8–10] While the importance of symptomatic bradycardia is widely recognised, the significance of recurrent ventricular pauses in bradycardiac episodes that are not clearly associated with symptoms is less clear. A 24 hour ambulatory electrocardiographic study by Bjerregaard of 260 healthy people found that ventricular pauses >1·5 s were common.[11] It has been suggested that while bradycardia is common in young people, especially at night, sinus pauses are a cause for concern in older people and should never exceed 2·5 s at any age.[12] Ventricular pauses in atrial fibrillation reflect extensive degeneration of pacemaker and conduction tissue.[13] Atrial fibrillation per se is known to reduce cerebral blood flow[14] and recurrent ventricular standstill would be likely to exacerbate this. Rebello and Brownlee showed that ventricular demand pacing may relieve dizziness as well as syncope in such patients.[2] Most of our patients continued to have symptoms even after treatment with digoxin was stopped or reduced.

Though the maximum exercise heart rate on placebo was not as high as in other studies,[15–17] it may have limited exercise duration. The maximum exercise heart rate was significantly reduced by xamoterol but not by low dose digoxin. Treatment with digoxin clearly increased the maximum ventricular pause beyond 2·04 s (93% CI: 2·2 to 2·8 s)—the longest pause in Bjerregaard's study—whereas xamoterol tended to reduce it to less than 2·1 s (95% CI: 1·5 to 2·1 s). Rebello and Brownlee thought that dizziness, which occurred in eight of our patients while they were being treated with digoxin, might suggest the need for pacemaker insertion.[2] Xamoterol, however, relieved dizziness in three and improved the symptom in four others, leaving only one unaltered. Elderly patients who are more liable to have atrial fibrillation are more likely to develop a slow ventricular response because of concomitant atrioventricular nodal disease.[18–20] This accords with the age of our patients (55 to 84) and the high incidence of conduction abnormalities on the electrocardiogram. The underlying heart disease too might have contributed to the conduction defects in our patients.

Digitalis is regarded as the best drug to control the ventricular response to atrial fibrillation.[21] At rest, vagal tone predominates and this may be enhanced by digoxin.[3] Increases in sympathetic tone during stress override the vagal effects of digoxin and limit its effect on the heart rate during exercise.[22] Increasing the dose of digoxin may well improve control of heart rate during exercise but it will exacerbate resting bradycardia.[23] β blockers and calcium antagonists tend to act preferentially on the exercise heart rate,[24 25] but both can exacerbate bradycardia,[16 26] and their negative inotropic effect detracts from their beneficial effect on the control of heart rate.[27 28] Interestingly, digoxin further depressed nocturnal bradycardia and this was consistent with an increase in vagal tone. Xamoterol increased nocturnal heart rate; this effect is consistent with an increased expression of the agonist activity of xamoterol at a time of low endogenous sympathetic activity.

Xamoterol decreased the number and duration of ventricular pauses in patients with sick sinus syndrome,[29] and gave better control of exercise heart rate.[30] On the other hand, xamoterol combined with digoxin gave better control of exercise heart rate than digoxin

Table 4 Comparative data from 24 hour ambulatory electrocardiography (mean (SEM))

	Placebo (Pl)	*p (Pl v X)*	*Xamoterol (X)*	*p (X v D)*	*Digoxin (D)*	*p (D v Pl)*
HHR max (beats/min)	139 (8)	NS	132 (8)	NS	131 (8)	NS
HHR min (beats/min)	50 (4)	<0·05	59 (5)	<0·001	45 (3)	NS
No of VP in 24 h	3322 (1443)	NS	2732 (1451)	<0·05	5238 (1707)	NS
Max VP in 24 h (s)	2·3 (0·1)	<0·005	1·8 (0·1)	<0·001	2·5 (0·1)	NS

HHR max, highest maximum hourly heart rate in 24 h; HHR min, lowest minimum hourly heart rate in 24 h; VP, ventricular pause.

alone.[30] These apparent actions of xamoterol are consistent with its selective β_1 partial adrenoceptor activity and are used to advantage in our patients. Xamoterol also seems to be of more benefit than digoxin in patients with mild to moderate heart failure who remain in sinus rhythm[31]; this may be relevant because heart failure often accompanies atrial fibrillation.[32]

Xamoterol is the best drug in patients with chronic atrial fibrillation who have episodes of bradycardia with ventricular pauses. Xamoterol reduces the duration and frequency of the pauses while improving the control of heart rate during exercise, and this is associated with an improvement in symptoms. Xamoterol may be especially useful in patients with mild heart failure; it must not be used in patients with severe heart failure.

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1 Pitcher DW, Papouchado M, James MA, Rees JR 24 hour ambulatory electrocardiography in patients with chronic atrial fibrillation *Br Med J* 1986,292·594

2 Rebello R, Brownlee WC. Intermittent ventricular standstill during chronic atrial fibrillation in patients with dizziness or syncope *PACE* 1987,10.1271–6.

3 Hoffman BF, Singer DH Effects of digitalis on electrical activity of cardiac fibres *Prog Cardiovasc Dis* 1964,7:226

4 Nuttall A, Snow HM. The cardiovascular effects of ICI 118,587 a beta$_1$-adrenoceptor partial agonist *Br J Pharmacol* 1982,77:381–8

5 Hashimoto T, Shiina A, Toyo-Oka T, Hosoda S, Kondo K The cardiovascular effects of xamoterol, a beta$_1$-adrenoceptor partial agonist, in healthy volunteers at rest *Br J Clin Pharmacol* 1986,21:259–65.

6 Harry JD, Marlow HF, Wardleworth AG, Young J. The action of ICI 118,587 (a beta$_1$-adrenoceptor partial agonist) on the heart rate response to exercise in man. *Br J Clin Pharmacol* 1981;12 266P–7P

7 Siegal S, Castellan NJ. *Nonparametric statistics for the behavioural sciences* 2nd ed. New York McGraw-Hill, 1988:168–89

8 Wang R, Camm J, Ward D, Washington H, Martin A Treatment of chronic atrial fibrillation in the elderly, assessed by ambulatory electrocardiographic monitoring. *J Am Geriatr Soc* 1980;28·529–34.

9 Salhadin P, Bran M, De Marneffe M, Denolin H Management of patients with chronic atrial fibrillation *Br J Clin Pharmacol* 1982,13·295S–6S.

10 James MA, Channer KS, Papouchado M, Rees JR. Improved control of atrial fibrillation with combined pindolol and digoxin therapy. *Eur Heart J* 1989,10·83–90.

11 Bjerregaard P Mean 24 hour heart rate, minimal heart rate and pauses in healthy subjects 40–79 years of age *Eur Heart J* 1983,4 44–51

12 Petch MC. Lessons from ambulatory electrocardiography. *Br Med J* 1985,291·617–8.

13 Mond HG, Sloman JG. Artificial cardiac pacemakers In. Hurst JW, Logue RB, Rackley CE, *et al*, eds. *The heart* 6th ed New York· McGraw-Hill, 1986 486–506

14 Corday E, Irving DW. Effect of cardiac arrhythmias on the cerebral circulation. *Am J Cardiol* 1960;6 803–8.

15 Roth A, Harrison E, Mitani G, Cohen J, Rahimtoola SH, Elkayam U. Efficacy and safety of medium- and high-dose diltiazem alone and in combination with digoxin for control of heart rate at rest and during exercise in patients with chronic atrial fibrillation. *Circulation* 1986,73. 316–24

16 Zoble RG, Brewington J, Olukotun AY, Gore R. Comparative effects of nadolol-digoxin combination therapy and digoxin monotherapy for chronic atrial fibrillation *Am J Cardiol* 1987,60·39D–45D

17 DiBianco R, Morganroth J, Freitag JA, *et al* Effects of nadolol on the spontaneous and exercise-provoked heart rate of patients with chronic atrial fibrillation receiving stable doses of digoxin. *Am Heart J* 1984;108:1121–7.

18 Zipes DP Specific arrhythmias: diagnosis and treatment. In Braunwald E, ed. *Heart disease*. 3rd ed Philadelphia WB Saunders, 1988:658–716

19 Orndahl G, Thulesius O, Hood B Incidence of persistent atrial fibrillation and conduction defects in coronary artery disease. *Am Heart J* 1972;84:120–31

20 Ostrander LD, Brandt RL, Kjelsberg MO, Epstein FH. Electrocardiographic findings among the adult population of a total natural community—Tecumseh, Michigan *Circulation* 1965;31:888–98.

21 Meijler FL. An 'account' of digitalis and atrial fibrillation. *J Am Coll Cardiol* 1985,5.60A–8A.

22 Goldman S, Probst P, Selzer A, Cohn K Inefficacy of 'therapeutic' serum levels of digoxin in controlling the ventricular rate in atrial fibrillation. *Am J Cardiol* 1975; 35 651–5

23 Redfors A Digoxin dosage and ventricular rate at rest and exercise in patients with atrial fibrillation. *Acta Med Scand* 1971,190:321–33.

24 David D, DiSegni E, Klein HO, Kaplinsky E Inefficacy of digitalis in the control of heart rate in patients with chronic atrial fibrillation beneficial effect of an added beta adrenergic blocking agent. *Am J Cardiol* 1978,44. 1378–82.

25 Klein HO, Kaplinsky E. Verapamil and digoxin· their respective effects on atrial fibrillation and their interaction. *Am J Cardiol* 1982,50 894–900.

26 Channer KS, Papouchado M, James MA, Pitcher DW, Rees JR. Towards improved control of atrial fibrillation. *Eur Heart J* 1987,8.141–7

27 Atwood J, Sullivan M, Forbes S, *et al* Effect of beta-adrenergic blockade on exercise performance in patients with chronic atrial fibrillation. *J Am Coll Cardiol* 1987, 10:314–20

28 Lewis RV, McDevitt DG Factors affecting the clinical response to treatment with digoxin and two calcium antagonists in patients with atrial fibrillation. *Br J Clin Pharmacol* 1988;25 603–6.

29 Tseu FL, Morley CA, Mackintosh AF. Xamoterol therapy for sick sinus syndrome [Abstract]. *Circulation* 1985, 72(part II).III–127

30 Molajo AO, Coupe MO, Bennett DH Effect of Corwin (ICI 118587) on resting and exercise heart rate and exercise tolerance in digitalised patients with chronic atrial fibrillation *Br Heart J* 1984,52:392–5

31 German and Austrian Xamoterol Study Group. Double blind placebo-controlled comparison of digoxin and xamoterol in chronic heart failure. *Lancet* 1988;1 489–93.

32 Kannel WB, Abbott RD, Savage DD, McNamara PM. Epidemiologic features off chronic atrial fibrillation: the Framingham study. *N Engl J Med* 1982;306·1018–22.

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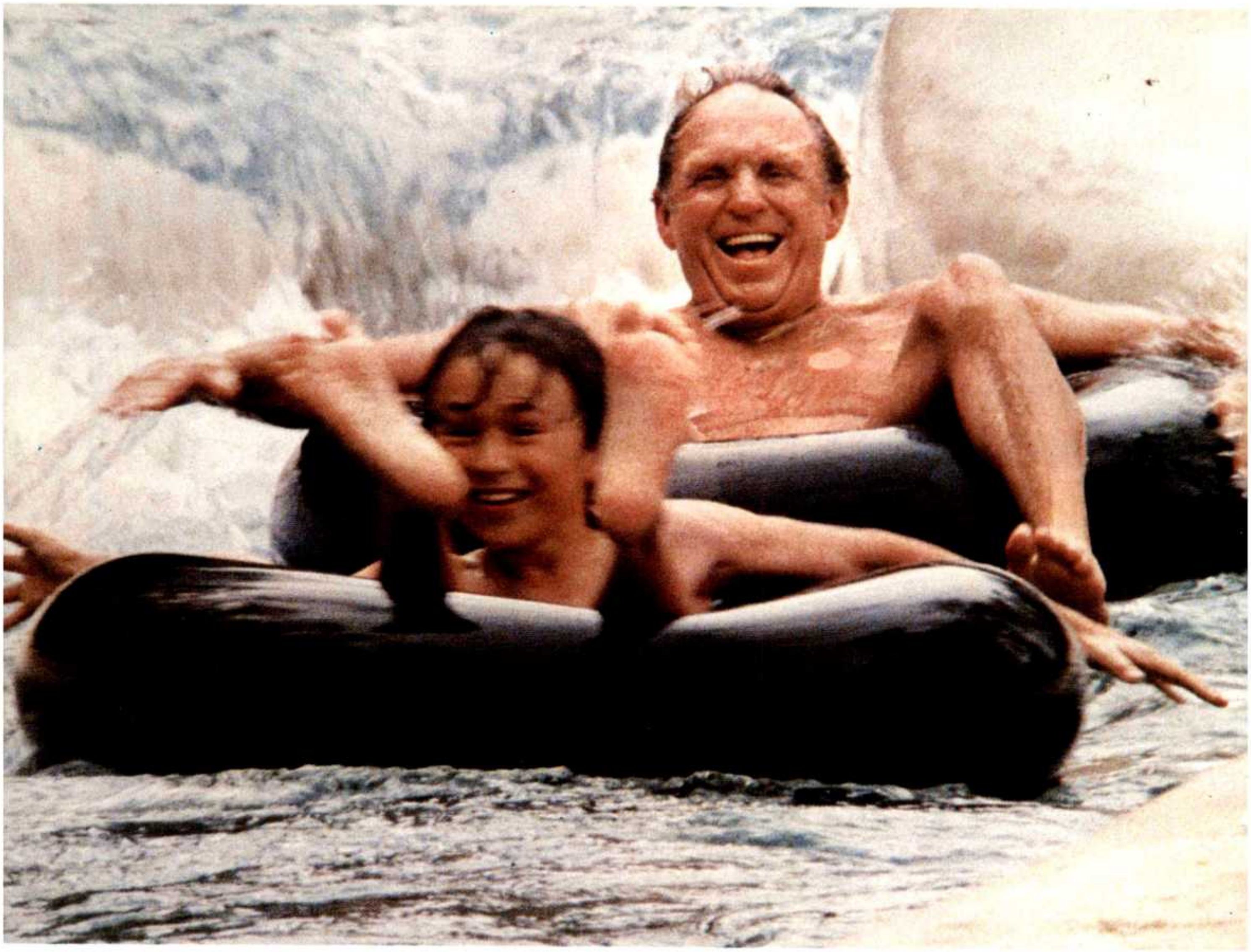

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Br Heart J 1990,64:261-5

Use of computed tomographic scanning and aortography in the diagnosis of acute dissection of the thoracic aorta

John M Morgan, Paul J Oldershaw, Huon H Gray

Abstract

Before the introduction of computed tomographic (CT) scanning, aortography was the investigation of choice for acute aortic dissection. Between 1978 and 1982, 24 patients were referred to the Brompton Hospital with suspected acute thoracic aortic dissection; all had aortography with diagnosis confirmed at surgery (n = 12) or necropsy (n = 2) or supported by clinical outcome (n = 8). One patient in whom aortography was negative had type B dissection at necropsy and another patient was lost to follow up. CT scanning became available in this unit in 1983 and between 1983 and 1987 was used as the only imaging investigation in 32 patients with suspected acute dissection of the thoracic aorta while in a further 22 patients aortography was used alone. Results were confirmed at surgery (n = 18), necropsy (n = 3), or supported by clinical outcome (n = 31). Two patients were lost to follow up. In an additional 16 patients both aortography and CT scanning were performed with concordant findings in 10. In six in whom the results were discordant, aortography was normal in three in whom subsequent CT scanning showed type B dissection and CT scanning was normal in three patients in whom aortography showed type A dissection.

Both CT scanning and aortography are reliable techniques for assessment of suspected acute dissection of the thoracic aorta. Both techniques misdiagnose occasionally and the frequency of misdiagnosis will be minimised by performing both investigations in patients where the level of clinical suspicion is high and the initial investigation negative. CT scanning tends to miss type A dissection and in view of the success of surgery in this condition this failing has the more serious clinical consequences.

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Acute dissection of the thoracic aorta is classified type A (affecting the ascending aorta) and type B (not affecting the ascending aorta).[1] Emergency surgical repair of type A dissection improves patient prognosis whereas immediate surgical intervention in type B, in the absence of complications, offers no survival advantage.[2 3] Until recently aortography was regarded as the investigation of choice for suspected acute dissection of the thoracic aorta[4] but the advent of computed tomographic (CT) scanning now offers an alternative, non-invasive means of diagnosis. We report a 10 year experience of the clinical assessment and investigation of acute dissection of the thoracic aorta by these two techniques.

Patients and methods

Between 1978 and 1987 94 patients were referred to the Brompton Hospital with suspected acute dissection of the thoracic aorta. We reviewed the case records, investigations, and outcome in these patients; follow up data on all patients were obtained by communication with referring physicians and general practitioners or by review at the Brompton Hospital.

STUDY DESIGN

Patients are considered in two eras, before and after the introduction of CT scanning to this hospital, to assess the impact of CT scanning on the investigation of acute dissection. Before CT (1978–1982) 24 patients were referred and all underwent aortography. In the five years (1983–1987) after CT scanning became available 70 patients were referred with suspected acute dissection of the thoracic aorta. Thirty two patients had CT scanning, 22 had aortography, and 16 patients had both.

We accepted the result of either investigation as correct if it was confirmed by surgical or necropsy findings. But if only those patients with surgical or necropsy confirmation of diagnosis were included the study population would show a preponderance of those with type A aortic dissection because it is the policy of this unit to recommend urgent surgery to such patients because of the poor prognosis of type A dissection with medical management alone. We took a prolonged event-free survival as supporting accurate diagnosis in patients with dissection who were managed medically, or those with negative investigations, and we paid particular attention to the clinical circumstances of death in such patients to assess the likelihood that a type A dissection was missed.

Results

AORTOGRAPHY 1978–1982

In 18 patients (eight female, 10 male; age 35–82, mean 68 years) aortography showed dissection of the thoracic aorta (table 1). Eight

Table 1 Initial diagnosis, management, and confirmation of diagnosis in patients presenting with suspected acute dissection of the thoracic aorta (ADA) between 1978 and 1982 and undergoing aortography

Patient No	*Result*	*Management*	*Confirmation of diagnosis*
1	Type A	Surgical	At surgery, type A
2	Type A	Surgical	At surgery, type A
3	Type A	Surgical	At surgery, type A
4	Type A	Surgical	At surgery, type A
5	Type A	Surgical	At surgery, type A
6	Type A	Surgical	At surgery, type A
7	Type A	Surgical	At surgery, type A
8	Type A	Surgical	At surgery, type A
9	Type B	Surgical	At surgery, type B
10	Type B	Surgical	At surgery, type B
11	Type B	Surgical	At surgery, type B
12	Type B	Surgical	At surgery, type B
13	Type B	Necropsy	At necropsy, type B
14	Type B	Necropsy	At necropsy, type B
15	Type B	Medical	Suggested by FU
16	Type B	Medical	Suggested by FU
17	Type B	Medical	Suggested by FU
18	Type B	Medical	None. lost to FU
19	No ADA	Medical	Suggested by FU
20	No ADA	Medical	Suggested by FU
21	No ADA	Medical	Suggested by FU
22	No ADA	Medical	Suggested by FU
23	No ADA	Medical	Suggested by FU
24	No ADA	Medical	Necropsy found type B

FU, follow up

Table 2 Initial diagnosis, management, and confirmation of diagnosis in patients presenting with suspected acute dissection of the thoracic aorta between 1983 and 1988 and undergoing CT scanning

Patient No	*Result*	*Management*	*Confirmation of diagnosis*
25	Type A	Surgical	At surgery, type A
26	Type A	Surgical	At surgery, type A
27	Type A	Surgical	At surgery, type A
28	Type A	Surgical	At surgery, type A
29	Type A	Surgical	At surgery, type A
30	Type A	Medical	No confirmation
31	Type B	Surgical	At surgery, type B
32	Type B	Surgical	At surgery, type B
33	Type B	Surgical	At surgery, type B
34	Type B	Medical	Suggested by FU
35	Type B	Medical	Suggested by FU
36	Type B	Medical	Suggested by FU
37	No ADA	Medical	Suggested by FU
38	No ADA	Medical	Suggested by FU
39	No ADA	Medical	Suggested by FU
40	No ADA	Medical	Suggested by FU
41	No ADA	Medical	Suggested by FU
42	No ADA	Medical	Suggested by FU
43	No ADA	Medical	Suggested by FU
44	No ADA	Medical	Suggested by FU
45	No ADA	Medical	Suggested by FU
46	No ADA	Medical	Suggested by FU
47	No ADA	Medical	Suggested by FU
48	No ADA	Medical	Suggested by FU
49	No ADA	Medical	Suggested by FU
50	No ADA	Medical	Suggested by FU
51	No ADA	Medical	Suggested by FU
52	No ADA	Medical	Suggested by FU
53	No ADA	Medical	Suggested by FU
54	No ADA	Medical	Suggested by FU
55	No ADA	Medical	Necropsy, no ADA
56	No ADA	Medical	Surgery, no ADA

patients had type A dissections and all these were managed surgically. Ten patients had type B dissections four of which were treated surgically and six medically. The diagnosis was confirmed in all 12 patients undergoing surgery. Of the six patients managed medically, one was lost to follow up, two had event-free survival of 66 and 77 months, and one died at five years (cause unknown). Two patients died within one month of diagnosis and in both of these the aortographic finding of type B dissection was confirmed at necropsy.

There were six patients (five male, one female; age 43–68, mean 59 years) with negative aortograms, three of whom had event-free survival at 60–120 (mean 80) months follow up. One patient died five years later of carcinoma of the breast. Two others died within one month of aortography. One of these had been admitted for investigation having developed hemiplegia and dysphasia, the clinical suspicion of dissection resting on an absent brachial pulse, and died in coma three days after admission without subsequent necropsy. The other patient died 24 hours after admission and at necropsy was found to have type B dissection. Thus this patient had a false negative aortogram.

AORTOGRAPHY OR CT SCANNING OR BOTH 1983–1987

CT scanning alone

There were 12 patients (two female, 10 male; age 54–81, mean 68 years) in whom CT scanning showed acute dissection of the thoracic aorta (table 2). Six patients had type A dissections and all but one were managed surgically. Three patients had type B dissections that required surgery because of complications and three patients had type B dissections that were managed medically. The diagnosis was confirmed in all patients undergoing surgery. Of the four patients managed medically, one elderly patient with a type A dissection was moribund on admission and died one hour later without surgery being attempted. Necropsy was not performed. The remaining three patients (type B dissection) had event-free survival at a follow up of 19–48 (mean 30) months.

There were 20 patients (10 male, 10 female; age 50–79 (mean 63) years) with negative CT scans, of whom 15 had event-free survivals of 2–66 (mean 24) months (table 2). Five patients have died. Two patients aged 72 and 79 years died in old peoples' homes 15 months and 30 months after investigation and necropsies were not performed. A third patient died four months after investigation of myocardial infarction; this diagnosis and absence of dissection were confirmed at necropsy. A fourth patient died in hospital during aortic aneurysmectomy and no aortic dissection was found at necropsy. The final patient died five years after investigation and the cause of death is unknown.

Aortography alone

There were 14 patients (three female, 11 male; age 27–73, mean 62 years) in whom aortography showed dissection of the thoracic aorta (table 3). Eight patients had type A dissections and all these were managed surgically. Six patients had type B dissections two of which were managed surgically and four medically. The diagnosis was confirmed in all 10 patients undergoing surgery. Of the four patients managed medically, two were lost to follow up and one had event-free survival at 60 months follow up. One patient died of an unrelated myocardial infarction one year after investigation and necropsy confirmed an old type B dissection.

There were eight patients (seven male, one female; age 61–73, mean 68 years) with

Table 3 Initial diagnosis, management, and confirmation of diagnosis in patients presenting with suspected acute dissection of the thoracic aorta between 1983 and 1988 and undergoing aortography

Patient No	*Result*	*Management*	*Confirmation of diagnosis*
57	Type A	Surgical	At surgery, type A
58	Type A	Surgical	At surgery, type A
59	Type A	Surgical	At surgery, type A
60	Type A	Surgical	At surgery, type A
61	Type A	Surgical	At surgery, type A
62	Type A	Surgical	At surgery, type A
63	Type A	Surgical	At surgery, type A
64	Type A	Surgical	At surgery, type A
65	Type B	Surgical	At surgery, type B
66	Type B	Surgical	At surgery, type B
67	Type B	Medical	Suggested by FU
68	Type B	Medical	Lost to FU
69	Type B	Medical	Lost to FU
70	Type B	Medical	Necropsy, type B
71	No ADA	Medical	Suggested by FU
72	No ADA	Medical	Suggested by FU
73	No ADA	Medical	Suggested by FU
74	No ADA	Medical	Suggested by FU
75	No ADA	Medical	Suggested by FU
76	No ADA	Medical	Suggested by FU
77	No ADA	Medical	Suggested by FU
78	No ADA	Medical	Suggested by FU

negative aortograms, seven of whom had event-free survival of 20–51 (mean 38) months (table 3). One patient, however, died 24 months later of myocardial infarction, confirmed by a rise in cardiac enzymes and the electrocardiogram. There was no clinical suspicion of dissection but no necropsy was performed.

CT SCANNING AND AORTOGRAPHY

When the first investigation (either CT scanning or aortography) was negative or gave insufficient information for clinical management and there was strong clinical evidence of dissection, a second investigation (CT scanning or aortography) was always performed. A total of 16 patients (12 male, four female; age 55–73, mean 64 years) underwent both investigations for this reason (table 4).

Both aortography and CT scanning negative

In eight patients, both investigations were negative and seven of these had event-free survival at follow up of 5–48 (mean 15) months. One was diagnosed as having a ventricular septal defect rather than dissection and died during surgical closure.

Table 4 Diagnosis, management, and confirmation of diagnosis in patients presenting with suspected acute dissection of the thoracic aorta between 1983 and 1988 and undergoing aortography and CT scanning

Patient No	*Aortography*	*CT*	*Management*	*Confirmation of diagnosis*
79	No ADA	No ADA	Medical	Suggested by FU
80	No ADA	No ADA	Medical	Suggested by FU
81	No ADA	No ADA	Medical	Suggested by FU
82	No ADA	No ADA	Medical	Suggested by FU
83	No ADA	No ADA	Medical	Suggested by FU
84	No ADA	No ADA	Medical	Suggested by FU
85	No ADA	No ADA	Medical	Suggested by FU
86	No ADA	No ADA	Medical	Surgery, no ADA
87	Type A	No ADA	Surgical	Surgery, type A
88	Type A	No ADA	Surgical	Surgery, type A
89	Type A	No ADA	Surgical	Surgery, type A
90	Type B	Type B	Surgical	Surgery, type B
91	No ADA	Type B	Medical	Necropsy, type B
92	No ADA	Type B	Medical	Suggested by FU
93	No ADA	Type B	Medical	Suggested by FU
94	Type B	Type B	Medical	Suggested by FU

Aortography or CT scanning or both positive

Eight patients had an abnormal CT scan or aortography. Four of these had CT scanning as the first investigation, with a negative result in three. There was a positive result in the fourth (type B dissection) but the CT scan gave insufficient information for further management. Aortography was therefore performed; it showed type A dissections in the three patients with negative CT scans, all of whom were referred for surgery (with confirmation of the diagnosis at operation). In the fourth patient aortography delineated the extent of the type B dissection. This patient was managed medically but later required surgery (when the diagnosis was confirmed) because of complications.

In four patients aortography was the first investigation and was negative in three. In the fourth patient aortography showed a type B dissection but further evidence that there was no type A dissection was considered necessary. CT scanning was therefore performed; it showed type B dissections in all. One patient, who was considered unfit for surgery despite clinical deterioration, died soon after admission, with necropsy confirmation of the diagnosis. The remaining three patients have had event-free survivals of 4–18 (mean 9) months.

In those patients in whom both CT scanning and aortography were required, the investigations were concordant in 10 patients and discordant in six. Aortography was negative in three patients in whom subsequent CT scanning showed type B dissection. In three patients CT scanning was negative, but subsequent aortography showed type A dissections.

Discussion

Before CT scanning became available aortography was the investigation of choice for suspected acute dissection of the thoracic aorta.[4] CT scanning is now available in most cardiac units in the United Kingdom and has been reported to be an effective alternative.[5 6] Most of the studies using both these techniques in the investigation of aortic dissection have been small and this has limited their value.[6 7] Oudberk *et al* reported a series of 26 patients undergoing CT scanning alone and found no misdiagnosis,[8] whereas Vasile *et al* reported a misdiagnosis rate of 5·2% in a series of 137 patients.[9] Streak artefact, difficulty in distinguishing aortic dissection from aortic aneurysm, absence of density difference between true and false lumens, and failure to manipulate window widths and levels were identified as major reasons for the errors in CT scanning. Aortography can also be erroneous as illustrated by Eagle *et al* who identified four false negative aortograms out of a series of 55 true negatives.[10] Some argue that CT scanning is the best investigation for the assessment of acute thoracic aortic dissection[11 12] while others argue that a negative CT scan does not remove the need for aortography.[13]

We sought to determine the accuracy of CT scanning and aortography in the investigation of patients referred with suspected acute dissection of the thoracic aorta and to determine their respective indications. It was not our intention to comment on the management of patients with proven dissection.

All 34 patients in our series who underwent surgery for acute thoracic aortic dissection had the preoperative diagnosis confirmed by surgery, and there were therefore no false positives in this group. Also there were no false positives in patients who died during the follow up period and in whom necropsy was performed (n = 4). To assess the possible frequency of false negative or erroneous results of CT scanning and aortography in patients whose management was medical (usually type B dissections) or those in whom no dissection was found, we looked for early deaths or suspicious clinical events during follow up. We accept that such an assessment must inevitably be imperfect because patients with an incorrect diagnosis may also have an event-free survival. The inclusion of any of these patients, were they known, would only increase the frequency of false negative or erroneous results. There were no suspicious events other than death and we therefore concentrated on those patients dying during follow up (n = 10) and tried to exclude dissection as contributing to the cause of death. This was often not possible but all cases in which the cause of death was not proven were reviewed.

In the era when only aortography was available (1978–1982) one patient died of unknown cause five years after being investigated and no further information was available. One patient was admitted for investigation of suspected dissection after having a cerebrovascular accident and died in coma. Aortography was negative but a necropsy was not performed and therefore we cannot exclude the presence of a dissection though a primary cerebral episode, rather than a neurological complication of dissection, seemed the most likely cause of death. Another patient died within one month of investigation and necropsy showed a type B dissection that had not been noted on the aortogram. This was a false negative result. In this patient the clinical findings were strongly suggestive of dissection, and CT scanning had it been available might have resulted in the correct diagnosis being made.

After the introduction of CT scanning there was an increase in the number of patients referred with suspected acute dissection of the thoracic aorta (70 patients in the five years 1983–1987 compared with 24 patients between 1978 and 1982). This could represent a true rise in the incidence of aortic dissection in the referral population but we think this unlikely. Referral patterns change over the years and we cannot exclude the possibility that the number of referring physicians increased. It seems more likely, however, that two other factors were mostly responsible. First, it has become increasingly widely appreciated that the prognosis of patients with type A dissection can be improved by immediate surgery. Second, physicians may be more likely to refer patients for a non-invasive investigation such as CT scanning when the level of clinical suspicion is relatively low rather than subjecting them to aortography which has been regarded by some to be potentially dangerous. The non-invasive nature of CT scanning is in our opinion its greatest advantage. On the other hand, aortography offers the ability to assess any aortic regurgitation and may demonstrate the entry and exit points of the intimal dissection and may thus contribute to surgical decisions on the most appropriate operation. It has been our policy not to perform coronary arteriography in patients with proven dissection (although we usually do perform this investigation if aortography is entirely normal and myocardial ischaemia is being considered as an alternative diagnosis) because we are unaware of any evidence that additional coronary bypass grafting at the time of surgery offers any prognostic or symptomatic advantage.

When CT scanning was available (1983–1987) the clinical outcome in four patients who had only one investigation (aortography or CT scanning but not both) was believed to require further comment. One patient had negative aortography and died two years later of a myocardial infarct. Necropsy was not performed but there was no clinical suspicion of dissection as a contributory cause of death. Three patients died some time after negative CT scans without subsequent necropsy and we cannot be certain that there was no evidence of previous aortic dissection. One of these patients died five years later; however, the other two died aged 72 and 79 years at 15 and 30 months after investigation, and in none of these three patients was there clinical suspicion of aortic dissection as a contributory cause of death.

The group of patients who were of particular interest were those 16 who had both CT scanning and aortography because there was considerable clinical evidence in the presence of a negative first investigation or because the first investigation had provided insufficient information for management decisions. In 10 the findings were concordant (eight had negative results with both investigations) but in six they were discordant. In this discordant group three patients had negative CT scans as the first investigation but were shown on aortography to have type A dissection; the aortographic findings were confirmed at surgery in all three. The other three patients in the discordant group had negative aortograms first but on subsequent CT scanning were shown to have type B dissection. All these patients are alive so as yet there is no confirmatory necropsy data but all had unequivocal CT appearances strongly suggesting falsely negative aortography.

So of the 62 aortograms performed on patients being admitted for investigation of suspected acute thoracic aortic dissection in the 10 years 1978–1987 at least four (6·4%) were falsely negative. All of these missed type B dissections. Of all the CT scans performed in the years 1982–1987 (n = 48) three (6·2%) were false negatives. All of these missed type A dissections. Because three patients were lost to follow up and eight died without necropsy or surgical confirmation of the diagnosis the true frequency of false negatives could be higher.

We found that any patient with clinically suspected acute thoracic aortic dissection should undergo aortography or CT scanning and that if this investigation is negative but the index of clinical suspicion high then the second investigation should always be performed. A negative first investigation with little clinical evidence of dissection should probably be regarded as sufficient to exclude the diagnosis. Whether aortography or CT scanning is performed as the first investigation is to a large extent dependent on individual circumstances such as the availability of each procedure, the experience of the person who will perform and report on whichever investigation is performed, and the restlessness of the patient (which will affect the quality of the CT scan). With CT scanning but not aortography patients with a low likelihood of dissection can be transferred from other hospitals for investigation and, if shown to have a normal scan, transferred back without being admitted. Our experience with patients in whom there is strong clinical evidence of dissection favours aortography as the first investigation because we were most concerned not to miss type A dissections. The promising experience reported with transoesophageal echocardiography in the investigation of suspected aortic dissection may contribute still further to reducing the likelihood of misdiagnosis.[14]

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1 Daily PO, Trueblood HW, Stinson EB, Wuerflein RD, Shumway NE Management of acute aortic dissection. *Ann Thorac Surg* 1970;10:237–40.

2 Miller DC, Mitchell RC, Oyer PE, Stinson EB, Jamieson SW, Shumway NE. Independent determinants of operative mortality for patients with aortic dissections *Circulation* 1984;70(suppl 3) I153–64.

3 Vecht RJ, Besterman EMM, Bromley LL, Eastcott HHG, Kenyon JR Acute dissection of the aorta· long term review and management *Lancet* 1980;i 110–3

4 Grossman W *Cardiac catheterisation and angiography* 3rd ed Philadelphia Lea and Febiger, 1986

5 Egan TJ, Neiman HL, Herman RJ, Malave SR, Sanders JH. Computed tomography in the diagnosis of aortic aneurysm dissection or traumatic injury *Radiology* 1980;136.141–6.

6 Thorsen MK, San Dretto MA, Lawson TL, Foley WD, Smith DF, Berland LL Dissecting aortic aneurysms. accuracy of computed tomographic diagnosis *Radiology* 1983,148:773–7.

7 Neumann CH, Guthaner DF, Wong DWH. Aortic dissection CT and angiographic comparisons. *Digitale Bilddiagn* 1984,4·14–7.

8 Oudkerk M, Overbosch E, Dee P CT recognition of acute aortic dissection *AJR* 1983;141 671–6

9 Vasile N, Mathieu D, Keita K, Lellouche D, Bloch G, Cachera JP Computed tomography of thoracic aortic dissection accuracy and pitfalls *J Comput Assist Tomogr* 1986,10.211–5.

10 Eagle KA, Quertermous T, Kritzer GA, *et al*. Spectrum of conditions initially suggesting acute aortic dissection but with negative aortograms *Am J Cardiol* 1986,57:322–6

11 Pariente RA, Couffinal JC, Wellers M, Farge C, Pradel J, Dologa M. Computed tomography versus aortography in diagnosis of aortic dissection *Cardiovasc Intervent Radiol* 1982,5:285–91

12 Singh H, Fitzgerald E, Ruttley MST. Computed tomography. the investigation of choice for aortic dissection? *Br Heart J* 1986,56.171–5

13 Danza FM, Fusco A, Falappa P. The role of computed tomography in the evaluation of dissecting aneurysms *Radiology* 1984;152·827–9.

14 Erbel R, Engberding R, Daniel W, Roelandt J, Visser C, Rennollet H, and the European Cooperative Study Group for Echocardiography. Echocardiograhy in diagnosis of aortic dissection *Lancet* 1989,i·457–66

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Abnormal diastolic function in patients with type 1 diabetes and early nephropathy

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Abstract

Left ventricular diastolic function was assessed by pulsed Doppler echocardiography in non-diabetic controls (n=11) and in patients with type 1 diabetes without microvascular disease (n=16; diabetic controls), with microalbuminuria (n=9), or with early persistent proteinuria (n=11). The peak filling velocities during the early and atrial phases of left ventricular diastole and their ratio (E:A ratio) were measured. All patients with diabetes had a normal serum concentration of creatinine and exercise electrocardiogram. The mean E:A ratio was significantly lower in those with proteinuria than in the diabetic controls because of an increase in peak atrial filling velocity; most patients with proteinuria had an abnormal E:A ratio of < 1·0. Multiple regression analysis showed that systolic blood pressure was the major determinant of both the peak filling velocity during the atrial phase of diastole and also left ventricular mass. Blood pressures were significantly higher in the proteinuria group than in the diabetic controls. Glycaemic control and autonomic function did not influence diastolic filling.

The slightly raised blood pressures at the earliest stages of diabetic nephropathy are sufficient to alter left ventricular diastolic compliance—this may reflect early hypertensive heart disease. These data do not preclude a specific heart muscle disease related to diabetes, but suggest that these slightly raised blood pressures contribute significantly to left ventricular dysfunction in these patients, in whom the risk of cardiovascular disease is already greatly increased.

The blood pressure begins to rise at the earliest stage of diabetic nephropathy,[1] and left ventricular hypertrophy (probably related to hypertension) is common once renal impairment develops.[2-4] Abnormal left ventricular diastolic function may be the earliest echocardiographic sign of hypertensive heart disease,[5,6] often occurring before appreciable left ventricular hypertrophy has developed.

In patients without diabetes, hypertensive left ventricular hypertrophy is an independent risk factor for cardiovascular morbidity and mortality.[4,7,8] The presence of blood pressure related diastolic abnormalities at the earliest stages of diabetic nephropathy might identify patients likely to benefit from early antihypertensive treatment.

Recently, pulsed Doppler echocardiography was used to assess diastolic function.[9,10] We used this technique to investigate the possibility that the slightly raised blood pressure associated with microalbuminuria and early proteinuria may influence left ventricular diastolic function.

Patients and methods

PATIENTS

We studied 39 white patients aged 20–60 with type 1 diabetes. They were selected according to urinary protein excretion and not according to blood pressure. None had evidence of renal disease other than diabetic nephropathy or received medication other than insulin. The mean albumin excretion rate was calculated from three timed overnight urine collections taken in the preceding 6–12 months. The following groups were studied:

Diabetic Controls Seventeen patients with fewer than three microaneurysms in each eye (on dilated fundoscopy by a single observer) and a mean albumin excretion rate in the normal range (< 10 μg/min).

Microalbuminuria Ten patients with a raised mean albumin excretion rate of between 30 and 200 μg/min.

Early persistent proteinuria Twelve patients with persistent Albustix-positive urine samples for between 6 months and 5 years, a 24 hour urinary protein loss of > 300 mg (on two occasions), and a normal serum creatine (< 106 μmol/l). None of these patients had received antihypertensive treatment before the study.

In addition, we studied 11 non-diabetic white individuals with no history of ischaemic heart disease or hypertension and on no treatment.

All patients gave informed consent to the procedures, which were approved by the hospital ethics committee.

Table 1 shows the clinical features of the groups. The mean albumin excretion rate was 6·6 μg/min in the diabetic control group and 56 5 μg/min in the microalbuminuria group. By definition, none of the patients in the diabetic control group had retinopathy but all of the other patients with diabetes had either background or proliferative retinopathy.

Table 1 *Clinical features of patients studied (mean (1 SEM))*

Feature	*Group* *Non-diabetic controls*	 *Diabetic controls*	 *Micro-albuminuria*	 *Proteinuria*
n	11	16	9	11
Age (yr)	34 (3)	35 (2)	38 (3)	34 (3)
Sex (M:F)	6:5	9:7	5:4	8:3
Diabetes duration (yr)	—	20 (2)	23 (3)	23 (2)
Body mass index (kg/m^2)	24·7 (1)	25·3 (1)	26·9 (1)	25·7 (0·5)
Glycated haemoglobin (%)	—	8·8 (0·5)	10·6 (0·7)*	10·3 (0·6)
Blood glucose (mmol/l)	—	13·5 (1·4)	9·9 (1·7)	12·1 (1·8)
Systolic pressure (mm Hg)	123 (4)	131 (4)	140 (6)	146 (2)†
Diastolic pressure (mm Hg)	80 (4)	81 (2)	86 (3)	94 (3)†
Heart rate (beats/min)	78 (3)	84 (4)	88 (5)	92 (5)
HRV (beats/min)	—	17·8 (2·3)	11·6 (2·8)	10·7 (1·5)
Valsalva ratio	—	1·52 (0·1)	1·32 (0·1)	1·35 (0·1)
HRR (beats/min)	—	20·4 (3·9)	16·2 (2·8)	13·8 (2·3)

*p < 0·05 *v* diabetic controls.
†p < 0·001 *v* diabetic and non-diabetic controls.
HRV, heart rate variability; HRR, heart rate response to standing.

METHODS

Glycated haemoglobin and blood glucose were measured in samples taken at the time of the echocardiogram. The albumin radioimmunoassay used has an intra-assay coefficient of variation of 6% at an albumin concentration of 2·5 mg/l and a normal range for non-diabetic individuals of 0·9–10 μg/min. Cardiovascular autonomic function was assessed in the patients with diabetes by the heart rate responses to deep breathing at 6 breaths per minute, to standing, and to the Valsalva manoeuvre.[11] The Valsalva ratio was not measured in one patient in each of the proteinuria and microalbuminuria groups because of recent vitreous haemorrhages. Autonomic function tests were performed after echocardiography.

Blood pressure was measured after 5 minutes' supine rest, at the time of the echocardiogram, by an observer who was unaware of the patient's echocardiographic data. Three readings were taken with a Hawksley random zero sphygmomanometer (Lancing, Sussex). Korotkoff phase V was regarded as the diastolic pressure. Mean values for systolic and diastolic pressure were calculated. No patient had a postural systolic fall in blood pressure of more than 10 mm Hg after 2 minutes of standing.

Bruce protocol treadmill exercise tests[12] were performed and analysed by standard criteria for ischaemia[13] in all patients with diabetes, but not in the normal control group. One diabetic control and one microalbuminuric patient had unequivocally abnormal exercise tests[14] and one proteinuric patient had a borderline abnormality with 1 mm planar ST segment depression. These three patients were excluded from the study; all other exercise tests were normal. In the remaining patients the mean exercise times and maximum achieved heart rates did not differ between groups.

All echocardiograms were performed and analysed by one observer (JBC), who was unaware of the patients' clinical state. A phased array system (Hewlett-Packard 77020A, Andover, Massachusetts, USA) was used with a 2·5 MHz duplex probe. Sector scans with colour flow mapping were used to screen for wall motion or valvar abnormalities; these were absent in all subjects. Pulsed Doppler recordings were made from the apical four chamber approach, with the sample volume level with the tips of the mitral valve leaflets in their maximum diastolic extent. We measured the peak left ventricular inflow velocities during the early (E vel) and atrial (A vel) phases of left ventricular diastolic filling, and the ratio of these two filling velocities (E:A ratio; fig 1). Mean values for each of these variables were calculated from 10 cardiac cycles to allow for respiratory variations.

Chamber dimensions and left ventricular thickness were calculated from M mode echocardiograms recorded according to American Society of Echocardiography recommendations.[14] Measurements of the intraventricular septal and posterior walls were plotted on age and body mass related nomograms,[14] and were considered to be increased if they lay above the relevant 95th centile. Left ventricular mass index was cal-

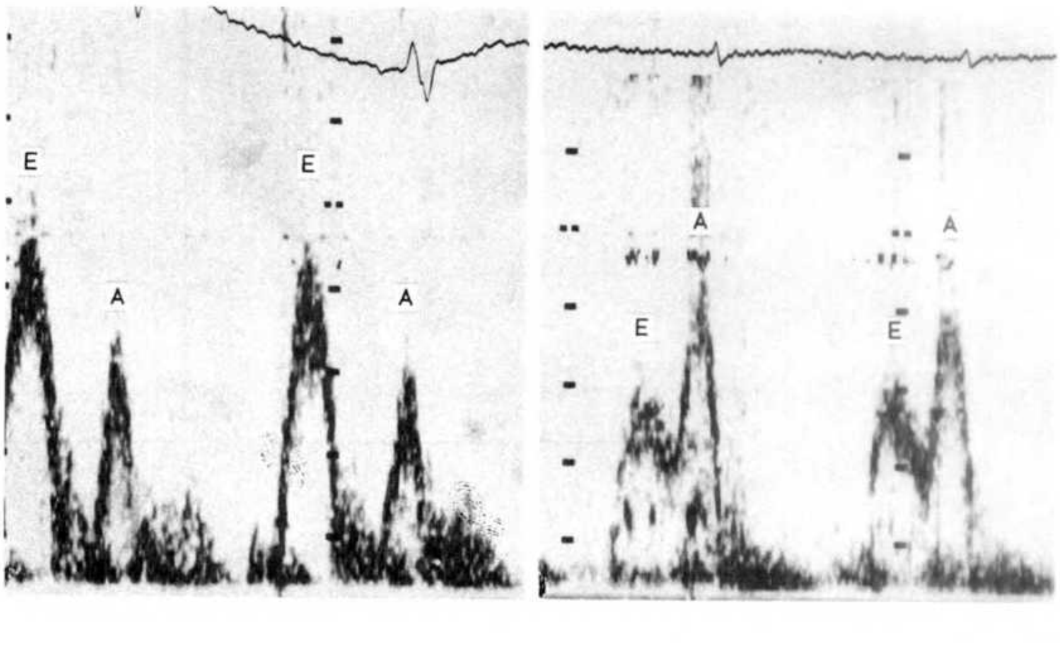


Figure 1 Pulsed Doppler echocardiograms recorded in a diabetic patient without microvascular complications showing the early passive peak in left ventricular filling (E) and the later active atrial phase (A). The right hand echocardiogram shows reversal of this pattern in a diabetic patient with proteinuria and mild hypertension.

culated from the method described by Devereux and Reichek[15] and left ventricular end diastolic volume from the Teicholz formula.

STATISTICAL ANALYSIS

The groups were initially compared by one way analysis of variance. Unpaired Student's *t* tests were performed if a significant ($p < 0·05$) difference was found by analysis of variance. Simple and stepped multiple regression analysis were used with A vel, E vel, the E:A ratio, and left ventricular mass as dependent variables. Systolic and diastolic blood pressures, age, heart rate, ventricular mass, left ventricular fractional shortening, glycated haemoglobin, blood glucose, and individual measures of autonomic function were included as subjective variables. Significance was taken to be $p < 0·01$ for multiple regression. Fisher's exact test was used where appropriate. All data are shown as mean (1 SEM).

Results

BLOOD PRESSURE, HEART RATE, AND GLYCAEMIC CONTROL

Blood pressure did not differ significantly between the control groups (table 1). Mean systolic and diastolic blood pressures increased progressively from both control groups to the proteinuria group and were significantly higher in the latter ($p < 0·001$). There was no significant difference in mean heart rate or blood glucose between the groups, although the mean concentration of glycated haemoglobin was significantly higher in the microalbuminuria group than in the diabetic controls.

AUTONOMIC FUNCTION

Mean heart rate variability, the Valsalva ratio, and heart rate response to posture tended to be lower in the microalbuminuria and proteinuria groups, but this trend was not significant (table 1). None of the patients studied had symptomatic autonomic neuropathy and only one patient in each group had abnormalities in all three tests of autonomic function. None had a postural systolic fall in blood pressure of > 10 mm Hg.

PULSED DOPPLER MEASUREMENTS

Mean E vel did not differ significantly between groups, but mean A vel was significantly higher in the proteinuria group than in the control groups ($p < 0·005$) (fig 2). This led to a significantly lower E:A ratio in the proteinuria group than in both control groups ($p < 0·05$). Three (18·8%) diabetic controls had an E:A ratio below 1·0 (fig 3) compared with four (44%) of nine in the microalbuminuria group ($p > 0·1$) and seven (64%) of 11 in the proteinuria group ($p < 0·05$). Seven of the 14 patients with an abnormal E:A ratio had mild intraventricular septal hypertrophy, and the intraventricular septum was significantly wider in the microalbuminuria and proteinuria groups than in the control groups (table 2). Left ventricular fractional shortening was higher in the proteinuria group than in the non-diabetic controls ($p < 0·001$), as was mean left ventricular mass, but not significantly so.

RELATION BETWEEN MEASUREMENTS

Table 3 shows the results of simple linear regression. Multiple regression showed:

(*a*) E vel was only independently influenced by age ($R^2 = 13·5\%$; $F_{1,45} = 7·0$; $p < 0·05$; NS).

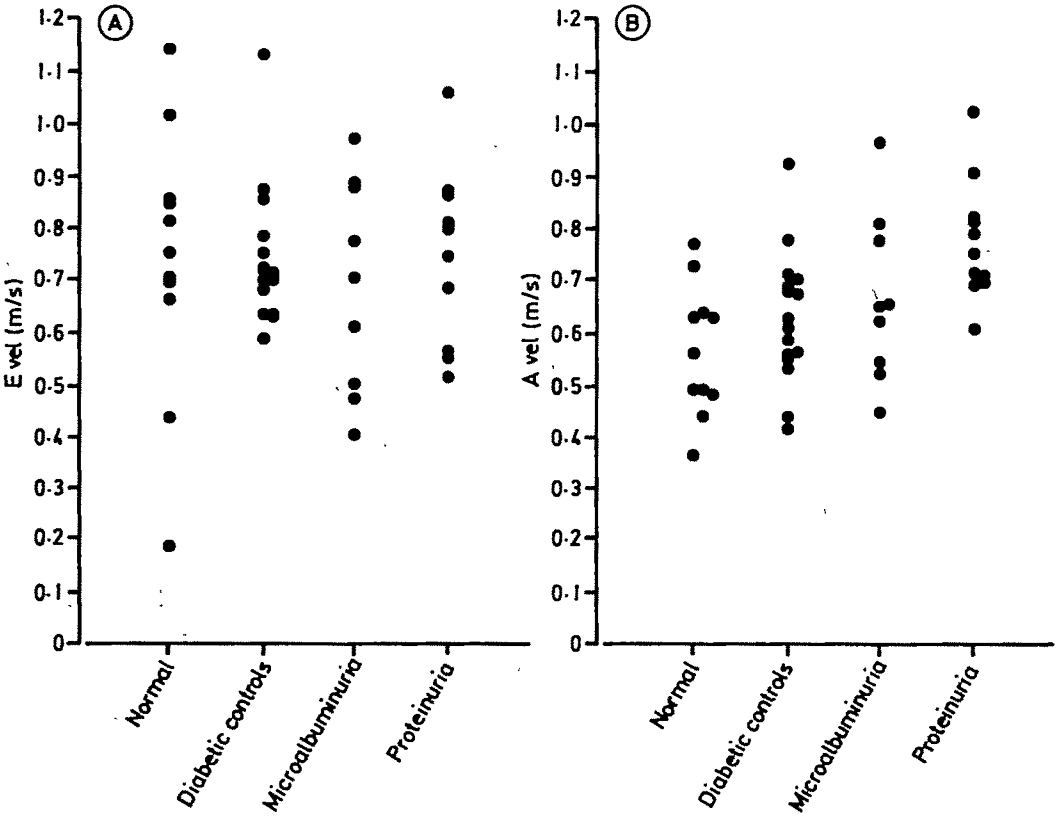


Figure 2 Values for peak left ventricular early filling (A) and atrial filling velocity (B) in normal controls and in the three diabetic groups In A there is an overlap of some values for the diabetic controls and patients with proteinuria.

Table 2 Echocardiographic data (mean (1 SEM))

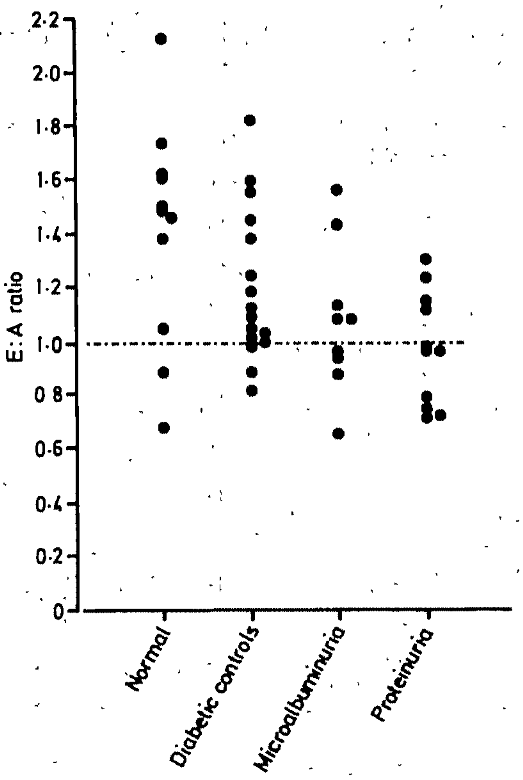
Variable	*Group* *Non-diabetic controls (n=11)*	*Diabetic controls (n=16)*	*Micro-albuminuria (n=9)*	*Proteinuria (n=11)*
E vel (m/s)	0·74 (0·1)	0·74 (0·03)	0·69 (0·07)	0·76 (0·06)
A vel (m/s)	0·56 (0·03)	0·63 (0·03)	0·67 (0·07)	0·78 (0·03)*
E A ratio	1·42 (0·1)	1·21 (0·08)	1·08 (0·1)	0·98 (0·06)†‡
Diastolic dimension (mm)	47 (1)	47 (1)	48 (1)	47 (2)
End diastolic volume (ml)	102 (4)	113 (6)	109 (8)	111 (9)
Septal width (mm)	9·7 (0·07)	9·8 (0·04)	11·7 (0·07)*	11·9 (0·08)*
LV mass (g/m)	87·(8)	101 (5)	115 (8)	113 (9)
Fractional shortening (%)	29 (2)	35 (2)	36 (3)	38 (2)§

*p < 0·005, diabetic and non-diabetic controls; †p < 0·05, *v* diabetic controls; ‡p < 0·0001, *v* non-diabetic controls; §p < 0·001, *v* non-diabetic controls.
E vel and A vel, peak early and atrial diastolic filling; E:A ratio, E vel/A vel, LV, left ventricular.

Table 3 Significant correlation coefficients (r) and probability values (p) where E vel, A vel, and the E.A ratio are dependent variables in simple linear regression

Variables	*E vel* *r*	*p*	*A vel* *r*	*p*	*E.A* *r*	*p*
Age	−0·46	0·001	—		0·36	0·05
Heart rate	—		0·42	0·005	0·42	0·005
Systolic blood pressure	—		0·53	0·0001	0·48	0·001
Diastolic blood pressure	—		—		—	
Ventricular mass	−0·37	0·05	—		—	
Duration of diabetes	—		—		—	
Fractional shortening	—		0·34	0·05	—	
End diastolic volume	—		—		—	
Glycated Hb	—		—		—	
Blood glucose	—		—		—	
Heart rate variability	—		—		—	
Valsalva ratio	—		—		—	
Heart rate response	—		—		—	

Figure 3 Values for the E.A ratio in normal controls and the three diabetic groups



(*b*) A vel was most influenced by systolic blood pressure ($R^2=28\%$; $F_{1,45}=17\cdot4$; $p < 0\cdot0001$) (fig 4) but also by heart rate ($R^2=8\cdot6\%$; $F_{1,44}=6\cdot0$; $p < 0\cdot05$; NS).

(*c*) The E:A ratios were only independently influenced by age and heart rate ($R^2=38\%$; $F_{2,44}=13\cdot6$; $p < 0\cdot0001$).

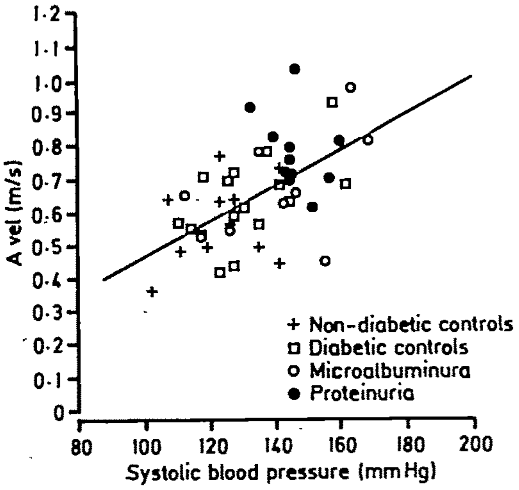


Figure 4 Relation between systolic blood pressure and the peak atrial phase of left ventricular diastolic filling (A vel) in the total study population (r=0·53, p < 0·0001, n=47).

(*d*) The ventricular mass was only influenced by systolic blood pressure ($R^2=21\%$; $F_{1,45}=12\cdot1$; $p < 0\cdot001$).

There was no significant relation between any measure of cardiovascular autonomic function or glycaemic control and diastolic filling.

Discussion

We have shown that the left ventricular filling pattern, as assessed by the E:A ratio, may be abnormal in the earliest stages of diabetic nephropathy—even if left ventricular hypertrophy is not considerable. The reduced E:A ratio was the result of an increased atrial component of diastolic filling, and systolic blood pressure was the principal influence on this measurement and also on left ventricular mass.

Only E:A ratios < 1·0 show an association with a reduced left ventricular filling rate on angiography[9] and the significance of small changes is unclear. Furthermore, left ventricular diastolic filling is influenced by several factors. Regional phase delays in ventricular relaxation, a raised left atrial pressure, alterations in preload,[16] the contractile state of the left ventricle,[17] and cardiovascular autonomic dysfunction[18] may all influence diastolic filling without any true change in left ventricular compliance. In the present study, however, the cardiac valves, wall motion, and left ventricular end diastolic volumes were normal in all patients or did not differ between groups. Though left ventricular fractional shortening was higher in the group with proteinuria than in the normal controls, on multiple regression this variable did not contribute significantly to any pulsed Doppler measurement. Finally, cardiovascular autonomic function had no influence on diastolic filling. Therefore, the differences in E:A ratio shown in this study almost certainly reflect differences in left ventricular compliance.

Left ventricular compliance depends on chamber size and geometry, wall thickness, and the mechanical properties of cardiac muscle.[19]

In this study systolic blood pressure was the principal correlate of left ventricular mass, and the mild hypertension present in very early nephropathy could affect the mechanical properties of the ventricle without significantly increasing left ventricular mass. There is supportive evidence from experimental hypertrophy caused by pressure overload in rats that such changes in ventricular compliance can occur independently of changes in ventricular wall thickness or mass.[20,21] These changes in the mechanical properties of the left ventricle could then presumably influence the pattern of left ventricular diastolic filling.

The patients with proteinuria had borderline hypertension (mean blood pressure 146/94 mm Hg); and diastolic function is often abnormal in non-diabetics with borderline essential hypertension.[5,6] An isolated increase in the peak atrial component of diastolic filling is also well described in such patients[3,22,23] and is often present before significant left ventricular hypertrophy develops.

An increased atrial contribution to diastolic filling in patients with diabetes has also been described[24,25] as has a relation between the sytolic blood pressure and diastolic function in those with type 1 diabetes.[26] However, it is unclear in these studies whether there is any relation between the diastolic abnormalities and blood pressure[24,25] or whether the abnormalities are confined to a subgroup with mild hypertension.[26]

There have been many other studies on diastolic function in diabetes, and many are difficult to interpret because the data on blood pressure, ischaemic heart disease, or renal function are frequently incomplete.[27–31] However, diastolic function was abnormal in normotensive patients with type 1 diabetes, without apparent coronary artery disease,[32–34] raising the possibility of a specific heart muscle disease in diabetes. The concept of such a "diabetic cardiomyopathy" was initially supported by epidemiological studies[35] that showed an increased incidence of congestive heart failure among the diabetic subjects in the Framingham cohort, although much of this could be accounted for by an excess of occult ischaemic heart disease. A series of necropsy studies, generally in those with type 2 diabetes,[36–38] many with renal impairment who had died in cardiac failure, are often used to support the existence of a specific diabetic heart muscle disease. The commonest pathological findings in these studies—an increased left ventricular mass, left ventricular hypertrophy, and increased interstitial and perivascular fibrosis, could equally well reflect preceding hypertension[39,40] or more severe hypertension in the diabetic group.[36] Most non-invasive studies on patients with diabetes have since failed to describe cardiac structural changes in the absence of hypertension,[34,41,42] and the results of myocardial biopsy studies in patients with diabetes are conflicting.[43–45] However, some data do suggest an increase in myocardial connective tissue in patients with diabetes without hypertension or coronary artery disease,[45] and this could theoretically influence diastolic compliance.[46] The question of a specific diabetic heart muscle disease requires a large correlative study of myocardial histopathology with both invasive and non-invasive assessment of cardiac function in well defined groups without coronary artery disease, hypertension, or microvascular disease.

Finally, we did not find any relation between diastolic filling and autonomic function in our patients, in contrast with the findings of other groups.[18,47] These groups showed that abnormal diastolic filling measured by radionuclide ventriculography[18] or digitised M mode echocardiography[47] was related to the degree of postural fall in systolic blood pressure,[18] and less so to measurements of heart rate variability.[18,47] In view of the preload dependence of diastolic filling,[16] some of the abnormalities described by these groups could be related to a reduced preload associated with postural hypotension. Other studies have failed to describe any relation between autonomic and diastolic function in patients with diabetes[31] or have failed adequately to correct for the high heart rate associated with autonomic neuropathy.[25]

In conclusion, we showed that in patients with type 1 diabetes, diastolic function is significantly abnormal in most patients by the stage of very early proteinuria. These abnormalities may be related to the mild hypertension seen in these patients. The present results do not preclude the existence of a specific diabetic heart muscle disease, but the presence of diastolic dysfunction (related in part to the raised blood pressure) at such an early stage of nephropathy, as well as mild left ventricular hypertrophy[48] re-emphasises the case for early antihypertensive treatment in these patients and for the increased use of echocardiography to detect those at risk.

1 Wiseman M, Viberti G, MacKintosh D, Jarrett RJ, Keen H. Glycaemia, arterial pressure and microalbuminuria in type I (insulin-dependent) diabetes mellitus *Diabetologia* 1984;26·401–5

2 Grenfell A, Monaghan M, Watkins PJ, McLeod AA. Cardiac hypertrophy in diabetic nephropathy—an echocardiographic study *Diabetic Med* 1988;5:840–4.

3 Thuesen L, Christiansen JS, Mogensen CE, Henningsen P. Echocardiographic-determined left ventricular wall thickness in insulin dependent diabetic patients. *Acta Med Scand* 1988;224 343–8.

4 Silberberg JS, Barre PE, Prichard SS, Sniderman AD Impact of left ventricular hypertrophy on survival in end stage renal disease. *Kidney Int* 1989;36.286–90.

5 Papademetriou V, Gottdiener JS, Fletcher RD, Freis ED Echocardiographic assessment by computer assisted analysis of diastolic left ventricular function and hypertrophy in borderline or mild systemic hypertension *Am J Cardiol* 1985,56:546–50

6 Snider AR, Gidding SS, Rocchini AP, *et al*. Doppler evaluation of left ventricular diastolic filling in children with systemic hypertension *Am J Cardiol* 1985,56·921–6.

7 Kannel WB, Sorlie P. Left ventricular hypertrophy in hypertension. prognostic and pathogenetic implications (The Framingham study) In. Strauer BE, ed *The heart in hypertension* (Boehringer-Mannheim symposium series). Berlin. Springer-Verlag, 1981:223–42

8 Casale PN, Devereux RB, Milner M, *et al*. Value of echocardiographic measurement of left ventricular mass in predicting cardiovascular morbid events in hypertensive men *Ann Intern Med* 1986;105.173–8.

9 Rokey R, Kuo LC, Zoghbi WA, Limacher MC, Quinones MA. Determination of parameters of left ventricular diastolic filling with pulsed Doppler echocardiography comparison with cineangiography. *Circulation* 1985; 71:543–50

10 Van Dam I, Fast T, De Boo T. Normal diastolic filling patterns of the left ventricle. *Eur Heart J* 1988;9:165–71.

11 Ewing DJ, Martyn CN, Young RJ, Clarke BF. The value of cardiovascular autonomic function tests 10 years experience in diabetes. *Diabetes Care* 1985;8:491–8

12 Bruce RA. Exercise testing of patients with coronary heart disease—principles and normal standards for discussion. *Ann Clin Res* 1971;**3**:323–33.

13 Goldschlager N, Selzer A, Cohn K. Treadmill stress tests as indicators of presence and severity of coronary artery disease. *Ann Intern Med* 1976;**85**:277–85.

14 Feigenbaum H. *Echocardiography*. 4th ed. Philadelphia: Lea and Febiger, 1986:621–39.

15 Devereux RB, Reichek N. Echocardiographic determination of left ventricular mass in man-anatomical validation of the method. *Circulation* 1977;**55**:613–8.

16 Stoddard MF, Pearson AC, Kern MJ, Ratcliff J, Mrosek DG, Labovitz AJ. Influence of alteration in preload on the pattern of left ventricular diastolic filling as assessed by Doppler echocardiography in humans. *Circulation* 1989; **79**:1226–36.

17 Bahler RC, Vrobel TR, Martin P. The relation of heart rate and shortening fraction to echocardiographic indexes of left ventricular relaxation in normal subjects. *J Am Coll Cardiol* 1983;**2**:926–33.

18 Kahn JK, Zola B, Juni JE, Vinik AI. Radionuclide assessment of left ventricular diastolic filling in diabetes mellitus with and without cardiac autonomic neuropathy. *J Am Coll Cardiol* 1986;**7**:1303–9.

19 Grossman W, McLaurin LP. Diastolic properties of the left ventricle. *Ann Intern Med* 1976;**84**:316–26.

20 Bing OHD, Matsoshita S, Fanburg BL. Mechanical properties of rat cardiac muscle during experimental hypertrophy. *Circ Res* 1971;**28**:234–45.

21 Alpert NR, Hamkell BB, Halpern W. Mechanical and clinical correlates of cardiac hypertrophy. *Circ Res* 1974;**35**(suppl 2):71–82.

22 Kuo LC, Quinones MA, Rokey R, Sartori M, Abinader EG, Zoghbi WA. Quantification of atrial contribution to left ventricular filling by pulsed Doppler echocardiography and the effect of age in normal and diseased hearts. *Am J Cardiol* 1987;**59**:1174–8.

23 Phillips RA, Caplan NL, Krakoff LR, *et al*. Doppler echocardiographic analysis of left ventricular filling in treated hypertensive patients. *J Am Coll Cardiol* 1987; **9**:317–22.

24 Takenaka K, Sakamoto T, Amano K. Left ventricular filling determined by Doppler echocardiography in diabetes mellitus. *Am J Cardiol* 1988;**61**:1140–3.

25 Airaksinen KEJ, Koistinen MJ, Ikaheimo A. Augmentation of atrial contribution to left ventricular filling in IDDM subjects as assessed by Doppler echocardiography. *Diabetes Care* 1989;**12**:159–61.

26 Danielsen R. Factors contributing to left ventricular diastolic function in long term Type 1 diabetic subjects. *Acta Med Scand* 1988;**224**:249–56.

27 Danielsen R, Nordrehaug JE, Lien E, Vik-Mo H. Subclinical left ventricular abnormalities in young subjects with long term Type 1 diabetes mellitus detected by digitised M-mode echocardiography. *Am J Cardiol* 1987; **60**:143–6.

28 Airaksinen J, Ikaheimo M, Kaila J, Linnaluoto M, Takkunen J. Impaired left ventricular filling in young female diabetics. An echocardiographic study. *Acta Med Scand* 1984;**216**:509–16.

29 Shapiro LM, Howat AP, Calter MM. Left ventricular function in diabetes mellitus. I: Methodology, and prevalence and spectrum of abnormalities. *Br Heart J* 1981;**45**:122–8.

30 Shapiro LM, Leatherdale BA, Mackinnon J, Fletcher RF. Left ventricular function in diabetes mellitus. II: Relation between clinical features and left ventricular function. *Br Heart J* 1981;5:129–32.

31 Sanderson JE, Brown DJ, Rivellese A, Kohner E. Diabetic cardiomyopathy? An echocardiographic study of young diabetics. *Br Med J* 1978;**i**:404–7.

32 Zarich SW, Arbuckle BE, Cohen LR, Roberts M, Nesto RW. Diastolic abnormalities in young asymptomatic diabetic patients assessed by pulsed Doppler echocardiography. *J Am Coll Cardiol* 1988;12:114–20.

33 Paillole C, Dahan M, Paycha F, Solal AC, Passa P, Gourgon R. Prevalence and significance of left ventricular filling abnormalities determined by Doppler echo cardiography in young type 1 (insulin dependent) diabetic patients. *Am J Cardiol* 1989;**64**:1010–6.

34 Fisher BM, Gillen G, Ong-Tone L, Dargie HJ, Frier BM. Cardiac function and insulin dependent diabetes: radionuclide ventriculography in young diabetics. *Diabetic Med* 1985;**2**:251–6.

35 Kannel WB, McGee DL. Diabetes and cardiovascular disease. The Framingham study. *JAMA* 1979;**241**: 2035–8.

36 Factor SM, Minase T, Sonnenblick EH. Clinical and morphological features of human hypertensive-diabetic cardiomyopathy. *Am Heart J* 1980;**99**:447–58.

37 Rubler S, Dlugash J, Yuceoglu YZ, Kumral T, Branwood AW, Grishman A. New type of cardiomyopathy associated with diabetic glomerulosclerosis. *Am J Cardiol* 1972;**30**:595–602.

38 Hamby RI. Diabetic cardiomyopathy. *JAMA* 1974; **229**:1749–54.

39 Moore GW, Hutchins GM, Bulkley BB, Tseng JS, Ki PF. Constituents of the human ventricular myocardium: connective tissue hyperplasia accompanying muscular hypertrophy. *Am Heart J* 1980;**100**:610–6.

40 Olsen EGJ. Hypertension, hypertrophy and dilation. *Postgrad Med J* 1972;**48**:768–9.

41 Gregor P, Widimsky P, Rostlapil J, Cervenka V, Visek V. Echocardiographic picture in diabetes mellitus. *Jpn Heart J* 1984;**25**:969–77.

42 Airaksinen KE, Ikaheimo MJ, Linnaluoto MK, Huikuri HV, Takkunen JT. Increased left atrial size relative to left ventricular size in young women with insulin dependent diabetes: a preclinical sign of the specific heart disease of diabetes? *Diabetes Res* 1987;**6**:37–41.

43 Fischer VW, Barner HB, Larose LS. Pathomorphologic aspects of muscular tissue in diabetes mellitus. *Hum Pathol* 1984;**15**:1127–35.

44 Sutherland CGG, Fisher BM, Frier BM, Dargie HJ. Endomyocardial biopsy pathology in insulin dependent diabetic patients with abnormal ventricular function. *Histopathology* 1989;**14**:593–60.

45 Nunoda S, Genda A, Sugihara N, Nakayama A, Mizone S, Takeda R. Quantitative approach to the histopathology of the biopsied right ventricular myocardium in patients with diabetes mellitus. *Heart and Vessels* 1985;1:43–7.

46 Hess OM, Schneider J, Koch R, Bamert C, Grimm J, Krayenbuehl HP. Diastolic function and myocardial structure in patients with myocardial hypertrophy. Special reference to normalized viscoelastic data. *Circulation* 1981;**63**:360–71.

47 Uusitupa M, Mustonen J, Laakso M, *et al*. Impairment of diastolic function in middle aged type 1 (insulin dependent) and type 2 diabetic patients free of cardiovascular disease. *Diabetologia* 1988;**31**:783–91.

48 Sampson MJ, Chambers J, Sprigings D, Drury PL. Intraventricular septal hypertrophy in type 1 diabetic patients with microalbuminura or early proteinuria. *Diabetic Med* 1990;**7**:126–31.

Br Heart J 1990;64:272–6

Doppler echocardiographic evaluation of pulmonary artery flow after modified Fontan operation: importance of atrial contraction

Shakeel Ahmed Qureshi, Roberto Richheimer, Roxane McKay, Robert Arnold

Abstract

Doppler echocardiography was used to evaluate blood flow in the pulmonary artery in 14 patients 2 to 42 months (mean (SD) 17 (12) months) after a modified Fontan operation incorporating a direct atriopulmonary anastomosis. Preoperatively six patients had tricuspid atresia, six had a double inlet left ventricle, and two had pulmonary atresia with an intact ventricular septum. The postoperative rhythm was sinus in 11 patients, junctional in one, ventricular pacing in one, and atrioventricular sequential pacing in one. In one patient the Doppler trace was unsatisfactory for analysis. In all patients forward flow in the pulmonary artery had biphasic peaks related to both atrial and ventricular contraction. The mean (SD) peak flow velocity that was synchronous with atrial contraction was 80 (30) cm/s and that synchronous with ventricular contraction was 74 (23) cm/s. The atrial contribution to total pulmonary artery flow, assessed by velocity-time integrals, varied between 22% and 73% (mean (SD) 45 (14)%). In patients with tricuspid atresia the mean (SD) peak flow velocity with atrial contraction was 90 (27) cm/s and that with ventricular contraction was mean (SD) 68 (24) cm/s. In patients with double inlet left ventricle the mean (SD) peak flow velocity was 67 (36) cm/s with atrial contraction and 80 (25) cm/s with ventricular contraction. The atrial contribution to total pulmonary blood flow in patients with tricuspid atresia was significantly higher (53 (11)%) than in those with double inlet left ventricle (37 (14)%).

Pulmonary artery flow after modified Fontan operation was biphasic and was related to both atrial and ventricular contraction. The atrial contribution to pulmonary blood flow is greater in patients with tricuspid atresia than in those with a double inlet left ventricle. The mechanism of the second peak related to ventricular contraction is unknown.

Several technical modifications of the original Fontan operation[1] have been used for physiological correction of patients with tricuspid atresia and double inlet left ventricle. These include the incorporation of a subpulmonary ventricular chamber,[2 3] valved conduits between the right atrium and pulmonary artery, vena caval valves, and direct non-valved atriopulmonary anastomosis.[4-6] There are conflicting reports on the importance of right atrial contraction, and therefore sinus rhythm, to the success of this operation.[7-9]

We assessed pulmonary artery flow patterns by Doppler ultrasound and evaluated the contribution of atrial contraction to total pulmonary blood flow after a modified Fontan operation with a direct non-valved atriopulmonary anastomosis.

Patients and methods

We studied 14 (eight boys and six girls aged 55–175 months (mean (SD) 90 (35) months at operation) randomly selected patients who underwent successful modified Fontan operation between December 1983 and June 1987 at the Royal Liverpool Children's Hospital. The Doppler echocardiographic study was performed between 2 and 42 months (mean (SD) 17 (12) months) postoperatively and the age at the study varied from 60 to 184 months (107 (37) months).

Six patients had tricuspid atresia. Four of these had associated pulmonary or subpulmonary stenosis and one had an absent pulmonary valve with intact ventricular septum. All five patients with reduced pulmonary blood flow had undergone palliative systemic-pulmonary artery shunts. The remaining patient had banding of the pulmonary trunk to reduce excessive pulmonary blood flow in infancy. Six patients had double inlet left ventricle. Two of the three with pulmonary or subpulmonary stenosis had been palliated with systemic-pulmonary artery shunts while three with unrestricted pulmonary blood flow had previous banding of the pulmonary trunk. Two patients had pulmonary atresia with intact ventricular septum. Both of these had undergone previous systemic-pulmonary artery shunts.

A direct posterior non-valved atriopulmonary anastomosis was constructed between the undivided superior vena cava, right atrium, and roof of the left atrium and the pulmonary arteries in 12 of the patients. In two patients an anterior anastomosis was constructed between the right atrial appendage and the pulmonary trunk/right pulmonary artery. In seven patients, the pulmonary trunk was divided and passed behind the aorta at the time of the repair, in five it was ligated, and in two

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the trunk and the pulmonary valve were left in continuity with the right ventricle.

In five patients with double inlet left ventricle the atria were partitioned by an oblique baffle that directed the pulmonary venous blood through both atrioventricular valves into the left ventricle. In one patient the right atrioventricular valve was closed.

Eleven of the patients were in sinus rhythm, one was in junctional rhythm, one in ventricular paced, and one in atrioventricular sequentially paced rhythm.

DOPPLER ECHOCARDIOGRAPHY

Cross sectional and Doppler echocardiography was performed using an Irex Meridian system. Cross sectional echocardiography was used to establish the optimal plane for pulsed Doppler sampling of the pulmonary artery flow distal to the atriopulmonary anastomosis. A 3·5 MHz phased array transducer with a pulsed Doppler frequency of 2 MHz was used for the examination. The optimum flow profiles in the pulmonary artery were obtained usually from the apical 4-chamber view or along the left sternal border, angling the transducer until the best audio signal was heard and the best spectral Doppler signal was displayed.

The Doppler velocity flow profiles were recorded at a paper speed of 75 mm/s. An electrocardiogram and phonocardiogram were recorded simultaneously with the Doppler spectral display to time the flow events. The recordings were made during quiet respiration in supine patients. Atrial contraction was defined on the traces from the P wave to the first heart sound on the phonocardiogram. The ventricular contraction (systole) was defined as the interval between the first and second heart sounds on the phonocardiogram. Peak velocities were measured as the modal peaks on the spectral traces. The traces were digitised around the modal velocities using the inbuilt software of the Irex Meridian system. The velocity waveform during atrial contraction was digitised and the velocity-time integral obtained in centimetres. This was separated from the flow during the remainder of the cardiac cycle by drawing a vertical line to the zero line at the beginning of the downstroke of the waveform of the atrial contraction. The total pulmonary blood flow was then similarly digitised to obtain the total velocity-time integral. No attempt was made to measure the atriopulmonary anastomotic diameter, which was assumed to be constant throughout the cardiac cycle. The atrial contribution to the total pulmonary flow was calculated as follows: 100 × (velocity-time integral of atrial contraction (cm), divided by velocity-time integral of total pulmonary flow (cm)). An average of at least five cardiac cycles was used for all measurements.

Doppler traces that were suitable for analysis were obtained in 13 of the 14 patients. The traces of one patient with pulmonary atresia and intact ventricular septum, described separately, were not included in the analysis because junctional rhythm precluded accurate timing of the atrial contraction. The patients were divided into two groups for the analysis; those with tricuspid atresia were compared (by unpaired t tests) with those with a double inlet left ventricle.

Results

In all the patients forward flow in the pulmonary artery had two peaks. Diastolic forward flow started at the second heart sound and was usually of low velocity. This was considered to be due to passive venous return into the pulmonary artery. Augmentation of the forward flow velocities then occurred; this began with the P wave, reached its peak between the P wave and the peak of the R wave, and returned to the baseline at the onset of the first heart sound. A second peak was seen during ventricular systole between the first and second heart sounds. In patients with tricuspid atresia the peak velocity after atrial contraction was higher than that after ventricular contraction; in contrast, in patients with double inlet left ventricle the pattern was reversed (fig 1A and B). In one patient with junctional rhythm the P wave was masked by the QRS complex. Peak forward flow in this patient occurred in early ventricular systole (due to atrial contraction) and a further peak occurred in ventricular diastole with passive venous filling (fig 2). In one patient with ventricular paced rhythm for postoperative complete heart block, there were, in addition to a dominant forward flow peak occurring with ventricular systole, separate peaks unrelated to ventricular systole and caused by atrial contraction (fig 3).

Peak flow velocity in the pulmonary artery synchronous with atrial contraction was

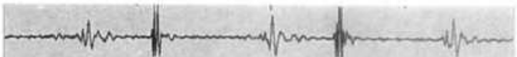

Figure 1 Doppler flow pattern in the pulmonary artery after Fontan operation showing biphasic flow in a patient with tricuspid atresia (A) compared with the pattern obtained in a patient with double inlet left ventricle (B).

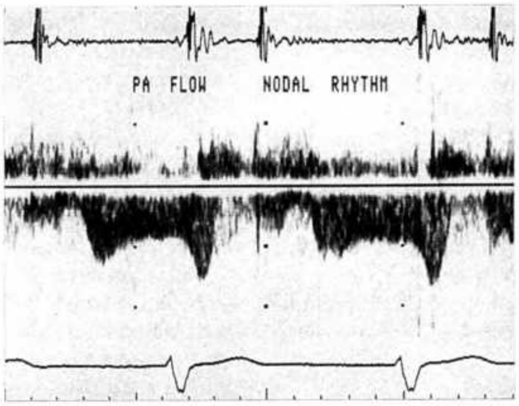

Figure 2 Doppler flow pattern in pulmonary artery in a patient with pulmonary atresia with intact ventricular septum in whom junctional rhythm developed after Fontan operation.

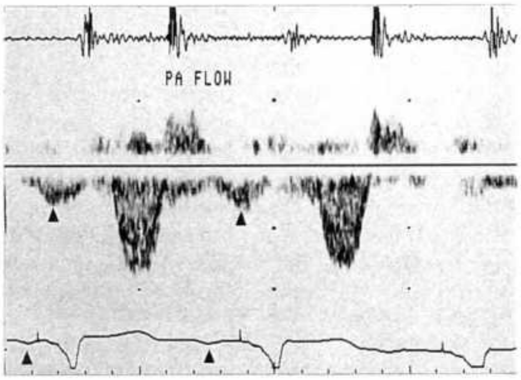

Figure 3 Doppler flow pattern in pulmonary artery in a patient with double inlet left ventricle in whom complete heart block developed after Fontan operation, and who had a ventricular pacemaker implanted (arrows indicate flow caused by atrial contraction).

27–123 cm/s (mean (SD) 80 (30) cm/s), while that during ventricular contraction was 46–109 cm/s (74 (23) cm/s). This difference was not significant at the 5% level.

In patients with tricuspid atresia the peak flow velocities during atrial contraction varied from 50 to 123 cm/s (90 (27) cm/s), compared with 28–113 cm/s (67 (36) cm/s) in those with double inlet left ventricle (p = 0·17). During ventricular contraction peak flow velocity was 46–99 cm/s (68 (24) cm/s) in patients with tricuspid atresia and 51–109 cm/s (80 (25) cm/s) in those with double inlet left ventricle (p = 0·42).

ATRIAL CONTRIBUTION

The table shows the atrial contribution to total pulmonary flow assessed from the velocity-time integral. This varied between 22% and 73% (45 (14)%).

In patients with tricuspid atresia the atrial contribution was 41–73 (53 (11)%) while in those with double inlet left ventricle it was 22–58% (37 (14)%). This difference was significant at the 5% level.

Atrial contribution to pulmonary blood flow

Tricuspid or pulmonary atresia		*Double inlet left ventricle*	
Case	*AC (%)*	*Case*	*AC (%)*
1	41	8†	22
2	43	9	26
3*	48	10‡	27
4	52	11	40
5	55	12	49
6	56	13	58
7	73		

*Before operation this patient had pulmonary atresia with intact ventricular septum.
†This patient had an atrioventricular sequential pacemaker.
‡This patient had a ventricular pacemaker.
AC, atrial contribution.

In one patient with pulmonary atresia and intact ventricular septum excision of the tricuspid valve and division of the pulmonary trunk were performed at the time of the modified Fontan operation to incorporate the hypoplastic right ventricle in the pulmonary circulation upstream to the atriopulmonary anastomosis. Doppler study showed that the atrial contribution to the total pulmonary blood flow was 48% and the flow pattern was similar to that in the patients with tricuspid atresia. Thus in this patient the incorporation of the hypoplastic ventricle did not affect the pulmonary flow pattern.

In two patients a hypoplastic right ventricle remained in continuity with the pulmonary circulation. One of them had pulmonary atresia with intact ventricular septum and a Waterston shunt. A transannular right ventricular outflow patch had been used to decompress the right ventricle. The hypoplastic tricuspid valve was closed at the time of the Fontan operation. When the Doppler study was carried out he was in junctional rhythm. The second patient had tricuspid atresia with an intact ventricular septum and no pulmonary valve. In both patients there was free regurgitation into the hypoplastic right ventricle.

The first patient had forward flow into the pulmonary artery during systole as a result of the atrial contraction, while the remaining forward flow occurred in mid and late diastole due to passive venous filling (fig 2). In the second patient Doppler flow traces were similar to those seen in patients with tricuspid atresia, the atrial contribution to the pulmonary flow being 41%. Thus the inclusion of a subpulmonary ventricular chamber as a reservoir distal to the atriopulmonary anastomosis did not seem to affect the flow pattern in the pulmonary artery.

Two of the patients with double inlet left ventricle had atrial contributions to pulmonary blood flow of 49% and 58%. Both these patients had higher preoperative mean right atrial pressures (>7 mm Hg) than the remaining patients with double inlet left ventricle.

Discussion

It has generally been accepted that sinus rhythm, and thus atrial contraction, is important for the success of the Fontan operation or its modifications,[5] although controversy continues as to whether the success is due to an improved left ventricular output or to a direct contribution of the right atrium to the pulmonary blood flow. The value of including a subpulmonary ventricular chamber in the repair is also controversial[2] and data from some recent studies suggest that atrial contraction may not be essential.[8 10] Indeed, in some complex defects, such as those in which the left atrioventricular valves are absent or hypoplastic or there are anomalies of venous drainage, total cavopulmonary connection has been proposed as an alternative to Fontan operation.[11] Nevertheless, the original or modified Fontan operation will continue to be used in most patients with tricuspid atresia or double inlet left ventricle. To characterise the type of pulmonary artery blood flow after a direct nonvalved atriopulmonary anastomosis we studied the Doppler flow patterns in these patients.

It is difficult to evaluate atrial function by a reliable technique. Doppler echocardiography gives a qualitative and possibly semiquantitative assessment of atrial function, however, by measurement of the ratio of forward flow during atrial contraction to the total flow in the pulmonary artery. Nakazawa *et al* suggested that the role of atrial contraction after the Fontan operation may be more important in those patients with a smaller pulmonary artery index, irrespective of whether they have tricuspid atresia or double inlet ventricle.[10] Conversely, in patients with a large pulmonary artery index, the right heart output may be less dependent on atrial contraction. These conclusions were based on an invasive study with a catheter mounted Doppler velocity probe. Volume flow is usually calculated from the mean velocity of flow and cross sectional area of the vessel where the flow velocity is measured. After the Fontan operation it is difficult to measure the area of the atriopulmonary anastomosis accurately. Because absolute values of volume flow may not be reliable, both we and Nakazawa *et al* have assumed this area to be constant throughout the cardiac cycle.[10] We have further adapted the intracardiac Doppler methods of flow assessments to the more conventional transthoracic pulsed Doppler techniques.

Shemin and associates, in an experimental study, reported that the right atrium did not function as a pump in the maintenance of pulmonary blood flow after a right atrium to pulmonary artery conduit.[12] Matsuda *et al,* in a study on dogs that had right atrium to pulmonary artery conduits with the right ventricle excluded from the pulmonary circulation, induced atrial fibrillation and found that both the systemic arterial pressure and pulmonary blood flow were maintained.[8] With atrial fibrillation, however, pulsatile flow in the atriopulmonary conduit was lost. Nakazawa *et al* evaluated seven patients after a Fontan operation for tricuspid atresia. They used pulsed Doppler echocardiography, cardiac catheterisation, and intracardiac Doppler with a catheter tipped velocity transducer.[7] They found that the flow patterns obtained by pulsed Doppler echocardiography were biphasic and identical to those obtained with a catheter tipped velocity transducer and that atrial contraction contributed to the forward flow of blood in the pulmonary artery. In a subsequent report, patients with a double inlet left ventricle were studied for comparison and similar flow patterns were obtained.[10] DiSessa *et al* also confirmed that the pulmonary artery flow was biphasic after the Fontan operation both in patients with tricuspid atresia and in those with double inlet left ventricle.[9] The flow, however, was not evaluated quantitatively or semiquantitatively. Alboliras *et al* suggested that synchronised atrial contraction was not necessary for adequate cardiac output, despite finding acceleration in pulmonary artery flow during atrial systole by Doppler.[13] Biphasic flow patterns in the pulmonary artery were reported by Hagler *et al,*[14] but, interestingly, in patients with reduced ventricular function the predominant flow occurred during ventricular systole.

Our measurements showed important differences between the patients with tricuspid or pulmonary atresia and double inlet left ventricle. The previous reports showed that the pulmonary artery flow was biphasic and these phases were related to atrial contraction and passive venous filling. In our study the second phase was consistently related to ventricular systole, which was followed by non-pulsatile low velocity flow caused by passive venous filling. These differences have not been emphasised before. We found that right atrial contraction, while contributing significantly to the total pulmonary blood flow in both groups of our patients, made a greater contribution to the pulmonary flow in patients with tricuspid atresia than in those with double inlet left ventricle. This may have been because higher atrial pressures cause greater right atrial hypertrophy. However, the mechanism of the second phase of flow that was synchronous with ventricular systole is not clear. DiSessa *et al* suggested that the second phase may have been the result either of right atrial relaxation and vena caval blood flowing into the pulmonary artery or filling of the left atrium from the pulmonary venous bed, which was in turn filled by flow from the pulmonary artery.[9] However, our study showed that this flow occurred only during ventricular systole and was also pulsatile. This suggests "active" rather than "passive" flow into the pulmonary artery. In one of our patients with double inlet left ventricle, in whom ventricular function was impaired, the atrial contribution (58%) to total pulmonary blood flow was higher than the rest of this group. While we found that Doppler echocardiography was useful in this study, it probably failed to detect slow and transient pulmonary regurgitation into the right atrium because of its very low velocity.

In conclusion, pulmonary artery flow after modified Fontan operation is biphasic. The atrial contribution to total pulmonary flow is greater in patients with tricuspid atresia than in those with a double inlet left ventricle. However, the importance of phasic pulmonary artery blood flow in the various subsets of patients and its long term effects on the pulmonary vasculature remain important questions for further investigation in a larger group of patients.

1 Fontan F, Baudet E. Surgical repair of tricuspid atresia *Thorax* 1971,26.240–8
2 Bull C, de Leval MR, Stark J, Taylor JFN, Macartney FJ Use of a subpulmonary ventricular chamber in the Fontan circulation *J Thorac Cardiovasc Surg* 1983;85:21–31
3 Kreutzer G, Galindez E, Bono H, de Palma C, Laura JP. An operation for the correction of tricuspid atresia. *J Thorac Cardiovasc Surg* 1973,66:613–21.
4 Kreutzer G, Vargas FJ, Schlichter AJ, *et al*. Atriopulmonary anastomosis. *J Thorac Cardiovasc Surg* 1982;83:427–36.
5 Choussat A, Fontan F, Besse P, Vallot F, Chauve A, Bricaud H. Selection criteria for Fontan's procedure In: Anderson RH, Shinebourne EA, eds. *Paediatric cardiology*. Edinburgh Churchill Livingstone, 1977:559–66.
6 Yacoub MH, Radley-Smith R Use of a valved conduit from

right atrium to pulmonary artery for "correction" of single ventricle. *Circulation* 1976;**54**:63–70.
7 Nakazawa M, Nakanishi T, Okuda H, *et al.* Dynamics of right heart flow after Fontan procedure. *Circulation* 1984; **69**:306–12.
8 Matsuda H, Kawashima Y, Takavo H, Miyamoto K, Mori T. Experimental evaluation of atrial function in right atrium-pulmonary artery conduit operation for tricuspid atresia. *J Thorac Cardiovasc Surg* 1981;**81**:762–7.
9 DiSessa TG, Child JS, Perloff JK, *et al.* Systemic venous and pulmonary arterial flow patterns after Fontan's procedure for tricuspid atresia or single ventricle. *Circulation* 1984;**70**:898–902.
10 Nakazawa M, Nojima K, Okuda H, *et al.* Flow dynamics in the main pulmonary artery after the Fontan procedure in patients with tricuspid atresia or single ventricle. *Circulation* 1987;**75**:1117–23.
11 De Leval MR, Kilner P, Gewillig M, Bull C. Total cavopulmonary connection: a logical alternative to atriopulmonary connection for complex Fontan operations—experimental studies and early clinical experience. *J Thorac Cardiovasc Surg* 1988;**96**:682–95.
12 Shemin RJ, Merrill WH, Pfeifer JS, Conkle DM, Morrow AG. Evaluation of right atrial-pulmonary artery conduits for tricuspid atresia. *J Thorac Cardiovasc Surg* 1979; **77**:685–90.
13 Alboliras ET, Porter CJ, Danielson GK, *et al.* Results of the modified Fontan operation for congenital heart lesions in patients with preoperative sinus rhythm. *J Am Coll Cardiol* 1985;**6**:228–33.
14 Hagler DJ, Seward JB, Tajik AJ, Ritter DG. Functional assessment of the Fontan operation: combined M-mode, two-dimensional and Doppler echocardiographic studies. *J Am Coll Cardiol* 1984;**4**:756–64.

VIEWS FROM THE PAST *Louis N Katz*

Louis N Katz (1897–1973) had a distinguished career as a physiologist in Carl Wiggers's department in Cleveland, Ohio. In 1924–25 he held a US National Research Council Fellowship at University College, London, in E H Starling's department, where he studied myocardial metabolism with A V Hill (the future Nobel laureate). The two months he spent with Thomas Lewis had a key influence, for after he became the founding director of the Michael Reese Cardiovascular Institute in Chicago in 1930 he made it into a renowned centre of electrocardiography. (Photograph provided by Dr Arnold M Katz.)

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Primary balloon dilatation of coarctation of the aorta in neonates

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Abstract

Primary balloon dilatation of coarctation of the aorta was attempted in 10 consecutive neonates (age range 2–23 days). The coarctation site was crossed and the balloon inflated in all but one patient. In two patients with associated severe isthmal hypoplasia there was no change in the gradient after dilatation. In the remainder, the residual gradients were trivial and angiography showed complete relief of coarctation.

Severe recoarctation developed 5–12 weeks after dilatation in five patients, each considered to have had an excellent initial result. The coarctation was rapidly progressive in three patients in whom Doppler studies within two weeks of the development of recoarctation had shown no significant gradient. In the other two patients progressive restenosis was charted by Doppler examinations over the course of 6–8 weeks. Three patients had a second, initially successful, dilatation procedure. One patient remained well with no residual gradient 18 weeks later. Stenosis recurred within eight weeks in the other two, and both have undergone successful surgical repair.

Balloon dilatation of a native coarctation of the aorta gave excellent immediate results in most neonates. Severe isthmal hypoplasia is, however, a contraindication to balloon dilatation and early restenosis is an important problem. These results do not support the continued use of primary balloon dilatation of coarctation of the aorta in neonates.

Balloon dilatation of the aorta is the chosen treatment for recoarctation of the aorta after surgical repair.[1–3] Its efficacy in the treatment of native coarctation is less well established. Variable success has been reported in infants and young children undergoing the procedure,[4–6] but follow up is necessarily short, and questions regarding the long term development of aortic aneurysm remain unanswered. To date there are only scattered reports of primary balloon dilatation of coarctation of the aorta in neonates presenting with severe coarctation in the first four weeks of life.[7–9]

We describe our early experience with this group of patients. Follow up is short, but early restenosis after complete early relief was common.

Patients and methods

Since December 1988, 10 consecutive neonates presenting to the Brompton Hospital with unoperated coarctation of the aorta have undergone attempted balloon dilatation of coarctation of the aorta. The median age at presentation was 10 (range 2–23) days and the mean (SD) weight was 3·2 (1 2) kg. The table shows patient details and associated anomalies. One patient had complete transposition of the great arteries, four patients had a small perimembranous ventricular septal defect, and one patient had a large doubly committed juxta-arterial ventricular septal defect thought to be suitable for primary repair if balloon dilatation were successful. At presentation none of the patients had femoral pulses. Three patients presented with cardiovascular collapse requiring resuscitation and prostaglandin infusion; the remainder presented with tachypnoea and poor feeding The full sequential diagnosis was established by cross sectional echocardiography in each patient. The maximum velocity across the coarctation site was recorded by continuous wave Doppler measurements and the peak instantaneous pressure gradient was calculated by the modified Bernoulli equation. These measurements were repeated 48 hours after the procedure and every two weeks during follow up.

Informed, written consent for cardiac catheterisation and possible balloon dilatation was obtained from the parents in each case. Cardiac catheterisation was performed with sedation and local anaesthesia in two patients and with general anaesthesia in the remainder. We used a percutaneous retrograde femoral arterial approach in all patients. In eight of the patients a size 7 French valved introducer was inserted 1–2 cm into the femoral artery and stabilised by immediate passage of the angiographic catheter. This technique enables multiple catheter changes, including the balloon dilatation catheter, with slight blood loss and damage to the artery. In two of the smallest patients a size 5 French valved introducer was inserted initially and the balloon dilatation catheter was later introduced percutaneously. All patients were given a loading dose of 50 IU of heparin/kg body weight when the introducer was inserted.

A size 5 French multipurpose catheter was used to cross the coarctation site and in general this procedure was uncomplicated. The pressure gradients before dilatation were thus recorded as the difference between the peak systolic pressure in the descending aorta before and the peak systolic pressure in the

Details of catheterisation data for each of the 10 neonates

Case no	*Age (days)*	*Symptoms*	*Associated abnormalities*	*Gradient before dilatation (mm Hg)*	*Gradient after dilatation (mm Hg)*	*Balloon (mm)*	*Weight (kg)*	*Outcome/follow up*
1	5	Cyanosis, tachypnoea	Transposition of great arteries, persistent ductus arteriosus	38	0	8	3·0	Successful anatomical correction 48 hours after dilatation, recoarctation at 8 wk, surgical repair
2	8	Mild tachypnoea	None	40	0	8	3·9	Recoarctation at 5 wk; repeat dilatation at 8 wk; restenosis—successful surgery
3	23	Poor feeding, tachypnoea	Small persistent ductus arteriosus; bicuspid aortic valve	38	8	8	3·7	Recoarctation at 6 wk, repeat dilatation at 9 wk; restenosis—successful surgery
4	2	Collapse—on prostaglandin E_2	Anomalous origin of left SCA, moderate perimembranous VSD	—	—	—	2·8	Unable to cross coarctation site
5	21	Tachypnoea	Perimembranous VSD	45	0	8	3·1	Follow-up 37 weeks: normal femoral pulses and Doppler echocardiography
6	9	Collapse—on prostaglandin E_2	Persistent ductus arteriosus	40	8	8	3·4	Gradual recoarctation; successful surgery
7	3	Poor feeding, tachypnoea	Large doubly committed subarterial VSD, isthmal hypoplasia	16	24	8	4·2	Unsuccessful procedure, isthmal dissection found at surgery; end-to-end anastomosis + PA banding
8	12	Cyanosis, poor feeding, pre-renal failure	Anopthalmia, musculoskeletal abnormalities	50	0	6	2·8	Follow-up 22 weeks: normal femoral pulses and Doppler
9	15	Tachypnoea, poor feeding	Small perimembranous VSD	16	4	8	3·1	Gradual recoarctation, successful 2nd balloon dilatation; follow up 22 weeks
10	3	Collapse—on prostaglandin E_2	Isthmal hypoplasia, perimembranous VSD; persistent ductus arteriosus	28	28	6	3·6	Referred for surgery, uneventful recovery

PA, pulmonary artery, SCA, subbclavian artery, VSD, ventricular septal defect.

ascending aorta after passage of the catheter through the coarctation site before angiography. In one patient it was impossible to cross the coarctation site because the catheter persistently followed the course of an anomalous right subclavian artery that arose from the descending aorta close to the site of coarctation. Angiography also showed a tortuous and hypoplastic aortic arch and isthmus.

After aortography the balloon catheter was passed over an exchange guidewire left in the ascending aorta. We used a balloon the same size as (or a little smaller than) the diameter of the aorta at the diaphragm measured from the cross sectional echocardiogram (table).[10] All balloons were carried on size 5 French catheters and were 15 mm long. After inflation to between four and eight atmospheres the balloon catheter was deflated and withdrawn, to leave the exchange wire in the ascending aorta. The size 5 French multipurpose catheter was then reinserted over the guidewire to enable repeat angiography and measurement of the pressure gradient on withdrawal.

All patients continued to be given a heparin infusion (400 IU/kg/24 h) for 24 hours after the procedure. One patient received an additional bolus of streptokinase and subsequent infusion because his leg was persistently pale and pulseless.

Results

In all patients severe preductal coarctation of the aorta was confirmed by aortography. The mean procedure time for the group was 68 minutes (range 33–118). In one patient it was impossible to cross the site of coarctation with the balloon catheter (see patients and methods).

The table shows the peak to peak systolic gradients measured before and after balloon dilatation in each patient. The mean (SD) systolic gradient before dilatation in the nine patients in whom balloon dilatation was attempted was 33 (13) mm Hg, falling to 7 (8) mm Hg ($p < 0{\cdot}001$, Student's t test) after dilatation. Patient 1 underwent successful anatomical correction of transposition of the great arteries 48 hours after the procedure.

In two patients the systolic gradient was unchanged after the procedure (see below for details). Selective ascending aortography after dilatation in the remainder showed excellent relief of coarctation in all, with no evidence of aneurysm formation. Minor irregularities of the vessel wall, particularly of the anterior surface of the aorta seen in lateral projection, were common (fig 1).

The peak instantaneous systolic gradient measured by Doppler aortography across the coarctation was recorded 48 hours after the procedure and was similar to the immediate post-dilatation gradients measured on catheter withdrawal (fig 2). In two patients (cases 7 and 10) there was no change in gradient after balloon dilatation. In patient 7, despite multiple balloon inflations with pressures >6 atmospheres, there was a persistent waist at the site of coarctation and no reduction in the gradient. This patient subsequently underwent surgical repair. At operation there was a severe dissection of the aortic isthmus with tears in the media and near rupture of the isthmus close to the coarctation site. Resection of the isthmus with an end-to-end anastomosis was performed. Subsequent recovery was uncomplicated. Review of the angiograms of this patient showed that the diameter of the balloon was 1 mm less than the diameter of the descending aorta at the diaphragm but 2 mm larger than at the hypoplastic isthmus. In the second patient there was a long tubular isthmal hypoplasia as well as discrete juxtaductal coarctation. The balloon diameter selected in this

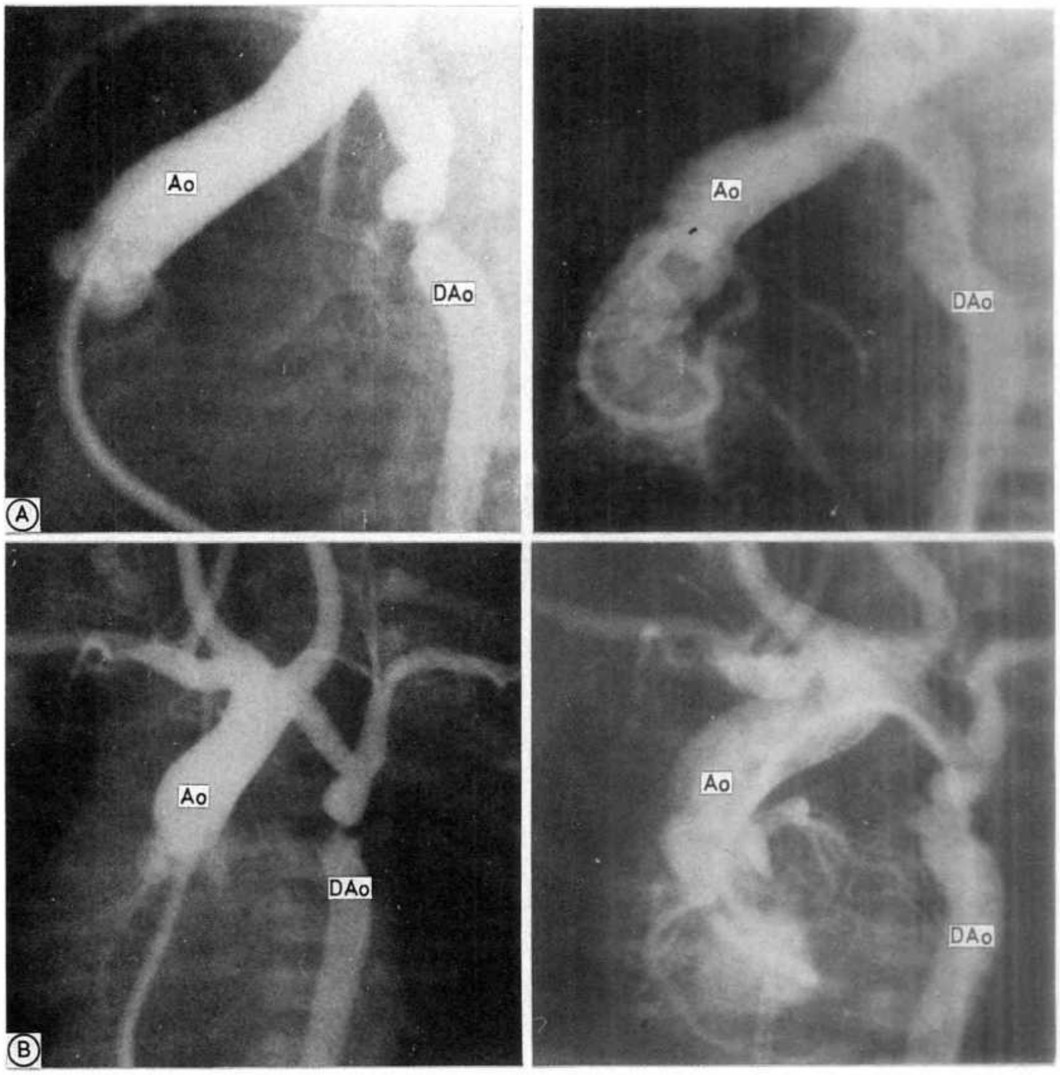

Figure 1 Angiograms of the ascending aorta recorded before (left) and after (right) balloon dilatation of a coarctation. There are minor irregularities of the aortic wall in both left anterior oblique (A) and lateral (B) angiographic projections.

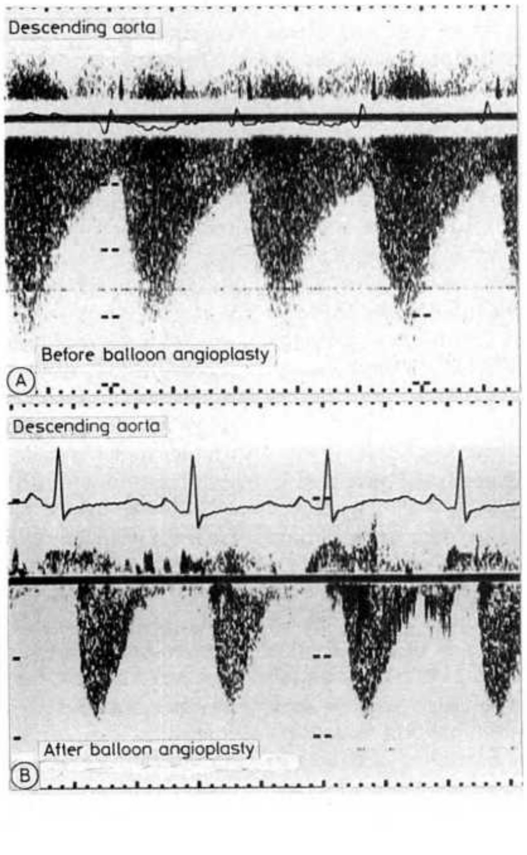

Figure 2 Continuous wave Doppler recordings of flow in the descending aorta before (A) and after (B) balloon dilatation of coarctation of the aorta in patient 2. The pre-dilatation recording shows the typical appearances of severe coarctation, with a prolonged diastolic gradient. The appearances after aortoplasty are normal.

patient was chosen so that it did not exceed the diameter of the narrowed isthmus. Angiography after balloon dilatation demonstrated improvement in the appearances at the coarctation site, but the gradient across the isthmus was unchanged. This patient has also made an uncomplicated recovery after surgery.

Only two of the remaining seven patients were symptom free 22 and 37 weeks after the procedure. Both had excellent femoral pulses and no significant residual systolic gradient measured by continuous wave Doppler. There was severe recoarctation in five of the patients. All of these patients had excellent initial relief of the coarctation with no significant residual gradient after balloon dilatation. In three of the patients, restenosis was rapid and severe five, six, and eight weeks after dilatation (see table). Clinical studies and Doppler aortography were normal two weeks to four weeks before the discovery of recoarctation in these patients. None of them had femoral pulses and Doppler-detected systolic gradients were 50, 64, and 90 mm Hg respectively.

In two further patients restenosis was slower and more progressive over 6–8 weeks.

Three of these patients underwent a second balloon dilatation procedure and in all of them

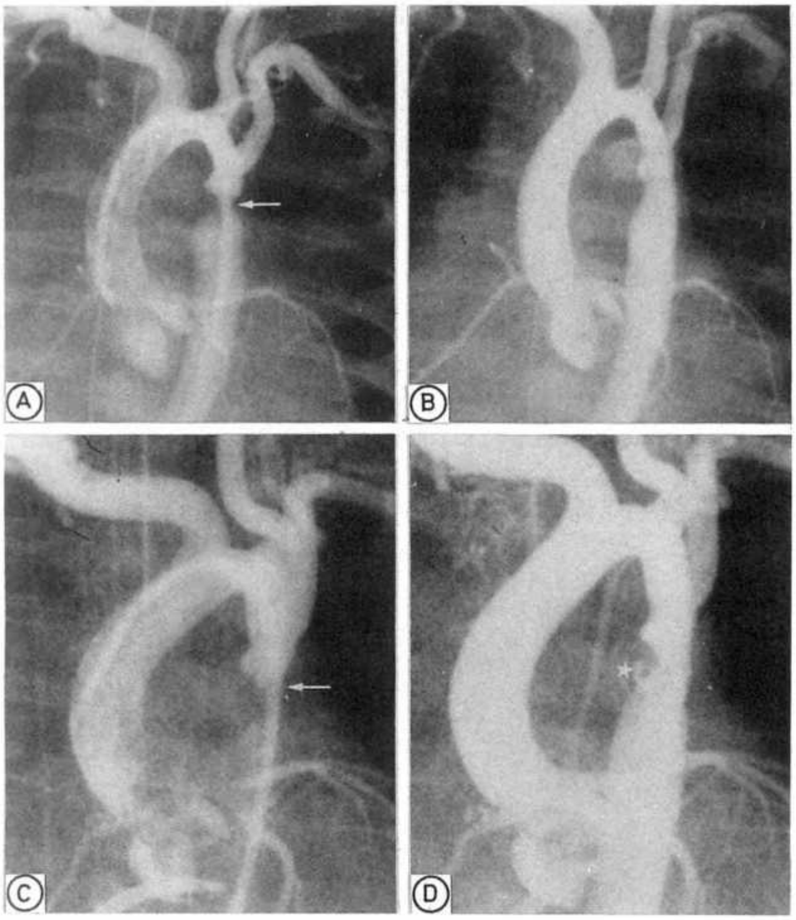

Figure 3 Serial left anterior oblique aortograms from patient 6. The top two panels show the appearances at original presentation (left) and the immediate result after balloon dilatation (right). Recoarctation occurred 6 weeks later (bottom left) and was successfully redilated (bottom right). A small intimal flap (*) was seen. Recoarctation occurred 8 weeks later and surgery was successful.

the gradient disappeared. Figure 3 shows sequential aortograms from one of these patients. One patient remains well with no evidence of restenosis 18 weeks later; in the other two patients recoarctation developed within eight weeks of the second procedure and they have undergone successful surgical repair. Two further patients who later presented with restenosis also had successful elective surgical repair with no attempt at a second balloon dilatation. The operative findings in these patients were indistinguishable from those of unoperated coarctation with no obvious sequelae from the earlier balloon dilatation.

Discussion

After the report by Sos *et al* of "successful" percutaneous balloon dilatation of unoperated coarctation in a neonate at necropsy,[11] there have been only scattered reports of primary balloon dilatation of coarctation of the aorta in children presenting in the first four weeks of life.[7-9] We report the results of balloon dilatation in 10 consecutive neonates presenting with severe coarctation of the aorta.

Our results showed that balloon dilatation relieved severe coarctation in most neonates in whom it was attempted; seven of the 10 neonates in our study had only trivial residual gradients and excellent angiographic appearances immediately after the procedure. We believe that it is not possible to make any technical or methodological changes to improve the initial result in these patients. None the less, the results for the group as a whole are disapponting. There were three early failures. In one it was impossible to cross the coarctation site because the left subclavian artery arose anomalously from the descending aorta and there was a tortuous aortic arch and isthmus. The other two early failures were in patients with moderately severe tubular hypoplasia of the isthmus. Severe dissection of the isthmus was found at subsequent operation in one of them. This almost certainly resulted from the use of a balloon with a diameter considerably larger than that of the isthmus, though smaller than that of the descending aorta at the diaphragm. A different mechanism was invoked in an earlier case when a dissecting aneurysm of the aortic arch was found at necropsy in a one day old child who had undergone balloon dilatation for severe coarctation and subsequently died during open chest aortic valvotomy.[12] These workers suggested that straightening of the balloon catheter within the hypoplastic arch explained the dissection that had occurred proximal to the narrowest part of the arch. Two conclusions can be drawn from this case and the experience with our two patients. First, we suggest that appreciable isthmal hypoplasia is a contraindication to balloon dilatation and secondly, while selection of balloon diameter according to the recommendations of Rao *et al* (that is, the same size or smaller than the descending aorta at the diaphragm)[10] is usually appropriate, care should be taken to avoid using a balloon with a bigger diameter than that of the aorta both proximal and distal to the site of discrete coarctation.

Perhaps more disappointing was the occurrence of early recoarctation in five of the seven neonates in whom an excellent immediate result had been obtained. Late restenosis several months after balloon aortoplasty in neonates was reported by others,[4 13] but the recoarctation in our patients was much earlier and rapidly progressive in three of them. All three of these patients had normal Doppler aortography and clinically normal femoral pulses 2–4 weeks before they presented with severe recoarctation. In the patients in whom surgical repair was undertaken, the findings were indistinguishable from the usual appearances of unoperated juxtaductal coarctation. While cicatrisation with fibrosis after the local trauma of balloon dilatation may be invoked in the patients with slowly progressive recoarctation, a more likely explanation, particularly in view of the time course of recoarctation, is that constriction of residual ductal tissue at the site of coarctation led to the more rapidly progressive restenosis in some of the patients. Indeed, the presence of a "sling" of ductal tissue encircling the aorta at the site of coarctation was shown by Ho and Anderson by detailed histological studies[14] and this mechanism has been invoked as a cause of early recoarctation after surgical repair. It must be more likely after balloon dilatation when the ductal tissue is neither incised nor removed.

Whatever the mechanism of restenosis, it is an important problem which taken with the early failure rate makes balloon dilatation unattractive in this group of patients. Particularly because surgical repair has a low mortality,[15] and when the subclavian flap technique was used there is a low incidence of recoarctation.[16] Thus, even in the absence of longer term follow up in the present series, we consider that surgical repair remains the best treatment for most neonates presenting with coarctation of the aorta.

Balloon dilatation of coarctation of the aorta can be performed in most neonates with a good early result. It is, however, unsuccessful and potentially dangerous in patients with associated isthmal hypoplasia. Furthermore, early restenosis is common, even when complete relief of coarctation is obtained. Though the technique may be useful when there are severe associated abnormalities, it cannot be recommended for general application in neonates with coarctation of the aorta.

1 Kan JS, White RI, Mitchell SE, Farmlett EJ, Donahoo JS, Gardner TJ. Treatment of restenosis of coarctation by percutaneous transluminal angiography. *Circulation* 1983;**68**:1087–94.
2 Saul JP, Keane JF, Fellows KE, Lock JE. Balloon dilation angioplasty of postoperative aortic obstructions. *Am J Cardiol* 1987;**59**:943–8.
3 Rao PS. Which aortic coarctations should we balloon dilate? *Am Heart J* 1989;**117**:987–9.
4 Lababidi ZA, Daskalopoulos DA, Stoekle H. Transluminal balloon coarctation angioplasty: experience with 27 patients. *Am J Cardiol* 1984;**54**:1288–91.
5 Wren C, Peart I, Bain H, Hunter S. Balloon dilatation of unoperated aortic coarctation: immediate results and one year follow up. *Br Heart J* 1987;**58**:369–73.
6 Morrow WR, Vick GW, Nihill MR, *et al*. Balloon dilation of unoperated coarctation of the aorta: short and intermediate-term results. *J Am Coll Cardiol* 1988;**11**:133–8.
7 Lock JE, Bass JL, Amplatz K, Fuhrman BP, Casteneda-Zuniga W. Balloon dilatation angioplasty of aortic coarctations in infants and children. *Circulation* 1983;**68**:109–16.
8 Finley JP, Beaulieu RG, Nanton MA, Roy DL. Balloon catheter dilatation of coarctation of the aorta in young infants. *Br Heart J* 1983;**50**:411–5.
9 Attia IM, Lababidi ZA. Transumbilical balloon coarctation angioplasty. *Am Heart J* 1988;**116**:1623–4.
10 Rao PS, Najjar HN, Mardini MK, Solymar L, Thapar MK. Balloon angioplasty for coarctation of the aorta: immediate and long-term results. *Am Heart J* 1988;**115**:657–65.
11 Sos T, Sniderman KW, Rettek-Sos B, *et al*. Percutaneous transluminal dilatation of coarctation of thoracic aorta post mortem. *Lancet* 1979;**iii**:970–1.
12 Krabill KA, Bass JL, Lucas RV, *et al*. Dissecting transverse aortic arch aneurysm after percutaneous transluminal balloon dilation angioplasty for an aortic coarctation. *Pediatr Cardiol* 1987;**8**:39–42.
13 Suarez de Lezo J, Fernandez R, Sancho M, *et al*. Percutaneous transluminal angioplasty for aortic isthmic coarctation in infancy. *Am J Cardiol* 1984;**54**:1147–9.
14 Ho SY, Anderson RH. Coarctation, tubular hypoplasia, and the ductus arteriosus. Histological study of 35 specimens. *Br Heart J* 1979;**41**:268–74.
15 Kopf GS, Hellenbrand W, Kleinman C, Lister G, Talner N, Laks H. Repair of aortic coarctation in the first three months of life: immediate and long-term results. *Ann Thorac Surg* 1986;**41**:425–30.
16 Nair UR, Jones O, Walker DR. Surgical management of severe coarctation of the aorta in the first month of life. *J Thorac Cardiovasc Surg* 1983;**86**:587–90.

CORRECTION

Editorial. ST segment changes as a surrogate end point in coronary thrombolysis *W Stewart Hillis, K J Hogg* (August issue: volume 64: pages 111–2)—The authors have asked us to point out that their address should have read: Department of Medicine and Therapeutics, University of Glasgow, Stobhill General Hospital, Balornock Road, Glasgow G21 3UW.

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TECHNOLOGY

Transoesophageal echocardiography in the longitudinal axis: correlation between anatomy and images and its clinical implications

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Abstract

Transoesophageal echocardiographic imaging in the longitudinal axis is a recent addition to the non-invasive evaluation of congenital and acquired heart disease. The technique provides unique images of intracardiac anatomy but their interpretation remains difficult. A heart specimen was therefore cut according to the echocardiographic imaging planes to elucidate the morphological details. The results suggested that longitudinal transoesophageal imaging complements the transverse axis approach. It gave new imaging information on the right ventricular outflow tract and the pulmonary trunk, the atrioventricular valves, the interventricular septum, the cardiac apex, and the thoracic aorta. In particular, it showed the entire length of the right ventricular outflow tract. When longitudinal imaging was used in combination with transverse imaging almost all the thoracic aorta could be examined. Imaging in the longitudinal axis may also allow better assessment of the mechanisms of atrioventricular valve regurgitation.

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Transoesophageal echocardiography is evolving rapidly as an investigative and monitoring technique in the outpatient clinic and the operating theatre.[1-3] Studies are usually performed with a probe that consists of a single, phased array transducer mounted at the tip of an adapted gastroscope. This produces cross sectional images in planes at right angles to the shaft of the probe. Standard transoesophageal probes thus produce short axis scans through the heart and great vessels, most of which show cardiac morphology in anatomical transverse planes.[4 5] This transoesophageal approach provides detailed insights into the systemic and pulmonary venous connections and into the morphology and function of the atria, the atrioventricular valves and each subvalvar apparatus, and the left ventricular outflow tract.[6-8]

Our experience of more than 1000 investigations, including some 200 in patients with congenital cardiac malformations shows that scanning in a single plane in the transverse axis displays certain regions of the heart poorly. These include the right ventricular outflow tract and the apical and trabecular components of the interventricular septum. Furthermore, much of the ascending aorta is inaccessible to transoesophageal imaging in the transverse axis because the trachea is interposed between the aorta and the oesophagus.

The potential of scanning from within the oesophagus has recently been extended by the introduction of biplane, phased array probes by Omoto and his colleagues.[9] These probes have a second transducer mounted at their tip that is oriented to scan in planes parallel to the shaft of the probe. Biplane transoesophageal probes therefore produce two cross sectional images in orthogonal planes, equivalent to transverse and longitudinal axis views of the heart. However, longitudinal axial scanning results in imaging planes that are unfamiliar.

To establish the anatomical basis for longitudinal transoesophageal echocardiographic imaging and to study its diagnostic potential we examined the morphological features of longitudinal anatomical sections of the heart and compared these with corresponding echocardiographic images obtained during clinical investigations.

Patients and methods

TRANSOESOPHAGEAL ECHO STUDIES

Transoesophageal imaging studies in both transverse and longitudinal planes were performed with a 5 MHz biplane transoesophageal probe connected to an Aloka SSD 870 ultrasound system. Studies were carried out on outpatients and during cardiac surgery. The probe was rotated to obtain a complete series of longitudinal images between one hilum and the other, as well as the full range of transgastric views and views of the descending aorta. We describe the manipulation of the probe for an operator who is facing the patient. Flexion of the probe in both anterior/posterior and lateral directions was used to optimise the image quality and increase the range of scan planes.

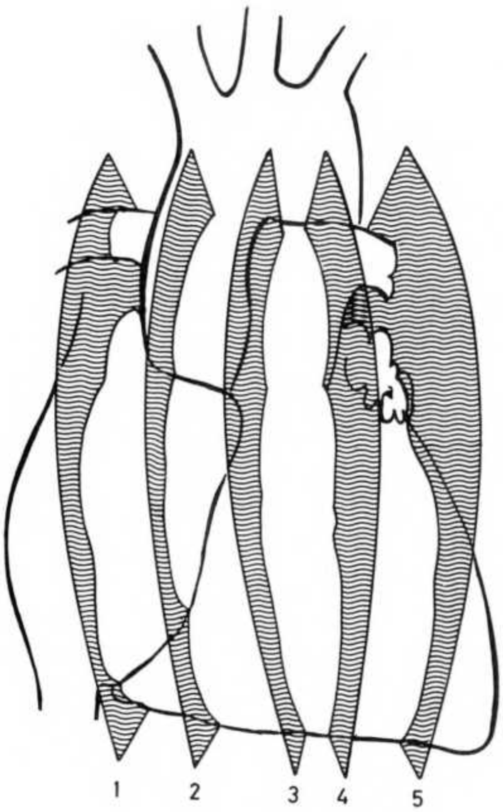

Figure 1 Diagram of the heart showing the orientation of five of the standard sections that are obtained by longitudinal transoesophageal imaging.

IMAGE ORIENTATION

The transoesophageal longitudinal axis scans, like the normal display of precordial images, are shown with the great arteries to the right side. The posterior aspect of the heart is displayed at the top of the image and the anterior aspect at the bottom, in keeping with the standard orientation of transoesophageal scans obtained in the transverse axis.

ANATOMICAL STUDY

A normal adult heart obtained at necropsy was perfused and fixed to preserve its shape. The proximal parts of the great vessels were retained, with the exception of the pulmonary arterial branches beyond the bifurcation. The specimen was first immersed in a waterbath (distilled water), and scanned in successive longitudinal planes from a point posterior to the left atrium, over the slight indentation caused by the oesophagus. These echocardiograms were performed with a standard precordial probe (short focus 5 MHz transducer in a plastic sleeve containing ultrasound gel, connected to a Toshiba SSH-160A machine) and the images were recorded on videotape. Black and white prints were taken of relevant sections. The ultrasound studies were used to plan the site and orientation of corresponding anatomical sections of the heart, which were then prepared and photographed.

The anatomical sections are displayed in a true anatomical orientation, with the base of the heart and the great vessels at the top.

Results

Imaging the heart in its longitudinal axis produces many echocardiographic cross sections that are unique. The fulcrum from which most of these views are obtained is determined by the position of the oesophagus at the back of the left atrium, but other unique longitudinal cross sections can be obtained from the fundus of the stomach. When the transducer is posterior to the left atrium, gradual rotation of the probe gives a series of fan shaped scans (fig 1). From right to left, these pass successively

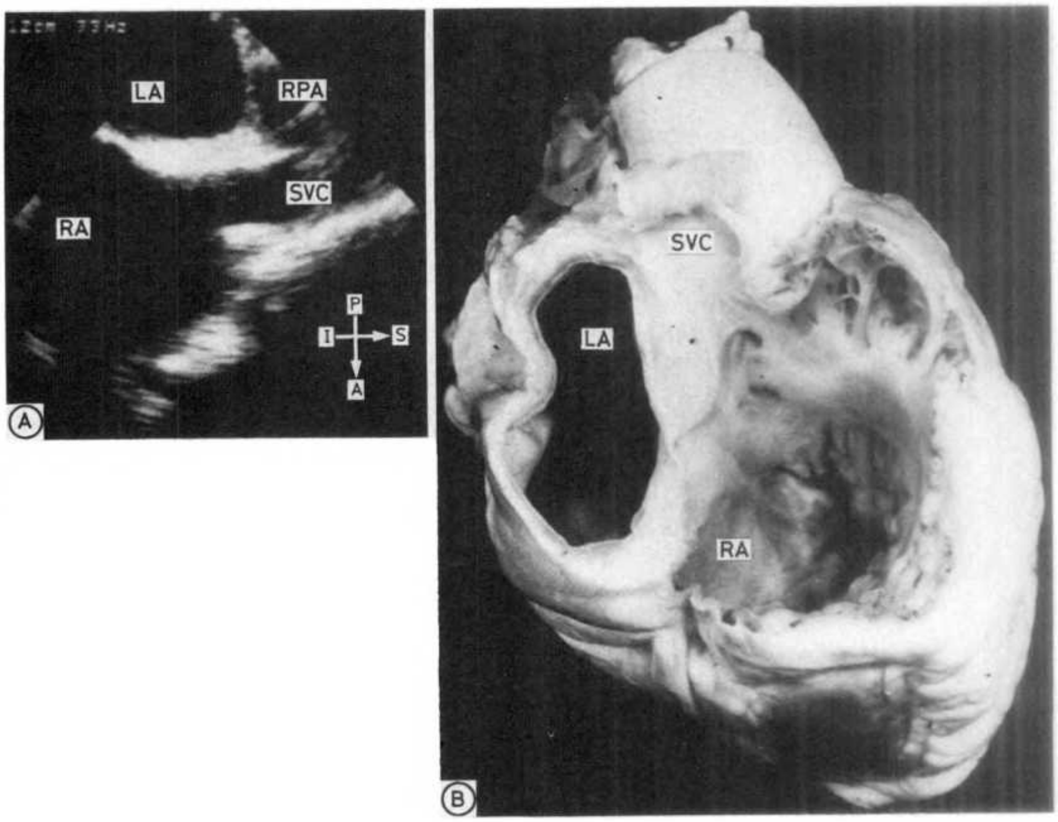

Figure 2 (A) Longitudinal axis scan through the right atrium at the site of drainage of the superior vena cava, corresponding to section 1 in fig 1. The image is displayed as it is seen on the echocardiographic monitor with the posterior aspect of the heart to the top and the cranial aspect to the right. The vein is cut in its long axis; posteriorly the right pulmonary artery (RPA) is shown in short axis. The oval fossa of the interatrial septum is shown on the left of the scan; fibro-fatty tissue causes the bright echo between the atrial walls. (B) The corresponding anatomical section as seen from the right lateral aspect of the heart. It is displayed in a true anatomical orientation, with the head to the top. LA, left atrium; RA, right atrium; SVC, superior vena cava; A, anterior; I, inferior; P, posterior; S, superior.

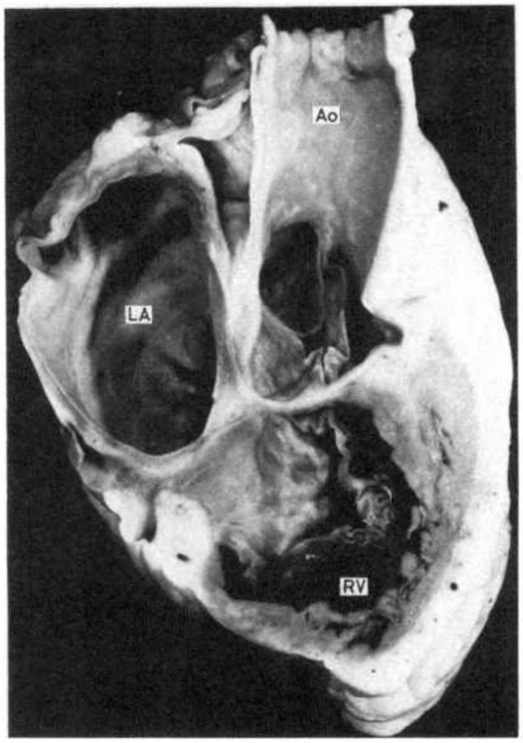

Figure 3 Longitudinal axis anatomical section corresponding to section 2 of fig 1. The ascending aorta (Ao) is shown in its long axis and the orifice of the right coronary artery is shown. The section also cuts the anterosuperior and inferior leaflets of the tricuspid valve, and the distal coronary sinus. LA, left atrium; RV, right ventricle.

through smaller portions of the right heart and larger portions of the left heart. Together these scans show important features of the atria, the atrioventricular valves, the ventricles, and the arterial trunks. In addition, longitudinal imaging with the interrogating scan plane directed laterally towards either of the pulmonary hila can show the pulmonary veins and pulmonary arterial branches in cross section.

We present the transoesophageal images and their anatomical correlates according to the standard sequential analysis of cardiac morphology, although in practice most longitudinal planes traverse at least three cardiac chambers.

RIGHT ATRIUM AND CONNECTIONS WITH THE VENAE CAVAE

When the ultrasound beam was directed towards the right side of the patient a long segment of the superior vena cava was displayed. It was displayed horizontally on the echocardiographic image (fig 2A). The connection of the superior vena cava with the right atrium was well displayed, and the right atrial appendage was seen anteriorly, cut obliquely near its base. Posteriorly the left atrium was cut in a longitudinal plane close to the orifices of the right pulmonary veins, while the right pulmonary artery was cut in its short axis. Because the junction of the inferior vena cava with the right atrium lies in a sagittal plane slightly to the side of the junction of the superior vena cava, its connection with the atrium could be displayed when the probe was inserted a little more deeply and rotated slightly in a clockwise direction. The distal segment of the coronary sinus was shown within the atrioventricular groove.

The anatomical section corresponding to this echocardiographic plane (fig 2B) showed, in addition, that the interatrial septum was traversed medially and anteriorly to the thin oval fossa. Apparent thickening of the atrial septum around its edge was caused by fat between the free walls of the atria, that is in Waterston's groove. The true interatrial septum was a thin structure in the region of the oval fossa (fig 2B).

TRICUSPID VALVE

Slight anticlockwise rotation of the probe produced a more medial section through the right atrium and brought the tricuspid valve into view. The anterosuperior leaflet was displayed to the right of the image and the mural (or inferior) leaflet to the left. It was difficult with longitudinal imaging to define the commissures of the tricuspid valve. The zone of coaptation was also not well seen, because a considerable portion of it lay in almost a longitudinal plane and therefore the leaflets could not be scanned tangentially to the closure line. The lateral component of the right ventricular cavity was shown anterior to the tricuspid valve (fig 3).

Further anticlockwise rotation of the probe produced longitudinal scan planes that traversed the muscular portion of the atrioventricular septum, which lies between the offset attachments of the mitral and tricuspid valve leaflets. Imaging of the smaller membranous portion of the atrioventricular septum was difficult because it lay in almost a longitudinal plane and was thus crossed at a very shallow angle.

Depending on the relative sizes and anatomical relation of the ascending aorta and the superior vena cava, longitudinal sections through the vein sometimes included an elliptical section of the right side of the anteriorly positioned ascending aorta. In all patients, the aorta was seen as the scan plane was shifted medially and the aortic valve was sectioned. The first cusps to be displayed were those within the right and non-coronary sinuses (fig 3). The orifice of the right coronary artery was also shown.

Longitudinal scans through the medial part of the tricuspid valve also brought the orifice of the coronary sinus into view, and the transverse sinus of the pericardial cavity was well seen between the posterior aspect of the aorta and the anterior wall of the left atrium.

RIGHT VENTRICULAR OUTFLOW TRACT

When the longitudinal axis transducer was positioned so that it scanned directly forward from the oesophagus in a true sagittal plane, the resulting imaging plane traversed the right ventricular outflow tract tangentially. If the tip of the probe was then angled to the right (fig 4A) the whole length of the right ventricular outflow tract was displayed together with the pulmonary valve, the proximal pulmonary trunk, and the anterolateral free wall of the right ventricle in the same view (fig 4B). The septal leaflet of the tricuspid valve was sometimes included in this section, and the atrioventricular portion of the membranous septum was crossed superiorly. The aortic root was located centrally in this view and all three cusps were sectioned (fig 4C).

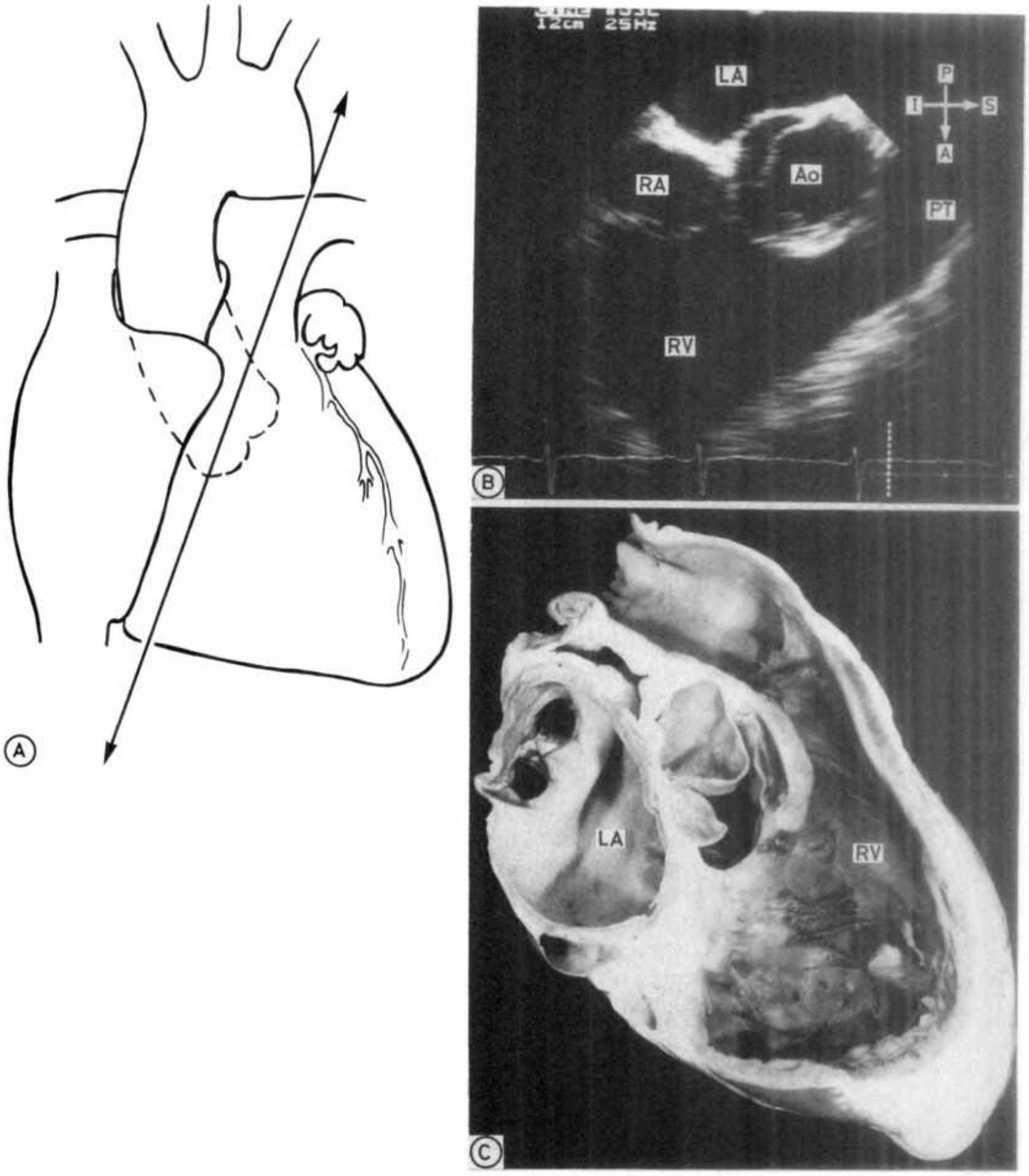

Figure 4 (A) Diagram showing the scan plane that displays the right ventricular outflow tract. This is obtained by tilting the transducer laterally from position 3 in fig 1. (B) Longitudinal axis scan through the right ventricular cavity (RV), the right ventricular outflow tract, and the proximal pulmonary trunk (PT). Centrally the aortic root (Ao) is cut obliquely. Postero-inferiorly, a segment of the right atrium (RA) is seen together with a portion of the atrioventricular junction and the antero-superior leaflet of the tricuspid valve. (C) A corresponding anatomical section. LA, left atrium. See fig 2 legend for other abbreviations.

Slight clockwise or counter-clockwise rotation of the probe from the central position used to scan the right ventricular outflow tract showed the pulmonary arterial branches near the bifurcation and these could be followed in cross section towards the hila. The right pulmonary artery was seen and displayed behind the ascending aorta, while the left pulmonary artery was seen above and in front of the left atrial appendage.

LEFT ATRIUM, MITRAL VALVE, AND LEFT VENTRICLE

When the probe was rotated in an anticlockwise direction from the longitudinal scans of the right heart towards the left, the left ventricle was first shown near the posteromedial commissure of the mitral valve, with the muscular portion of the ventricular septum crossed tangentially (fig 5). The apical part of the right ventricle was shown as a rim anteriorly and the muscular septum was shown in oblique section. A small portion of the interventricular component of the membranous septum was still visualised cranially.

Continued anticlockwise rotation could be used to study the coaptation of the leaflets of the mitral valve in longitudinal planes. Between the posteromedial commissure and the middle of the leaflets, these planes crossed the zone of coaptation approximately at right angles to the apposed edges of the leaflets (fig 6). More laterally, the imaging planes became more or less parallel to the zone of coaptation as it curved upwards towards the left atrial appendage. Thus with longitudinal imaging the relations between the leaflets over their lateral thirds and near the anterolateral commissure are difficult to ascertain. Indeed, the space between the middle and lateral scallops of the mural (posterior) leaflet could be confused with the zone of coaptation. Because the papillary muscles lie almost in the same longitudinal plane, they may be seen together on one echocardiographic image.

The left ventricular outflow tract was cut obliquely when it was assessed in a series of longitudinal scans. Continuity between the leaflets of the aortic and mitral valves and the left coronary sinus of the aorta could be shown

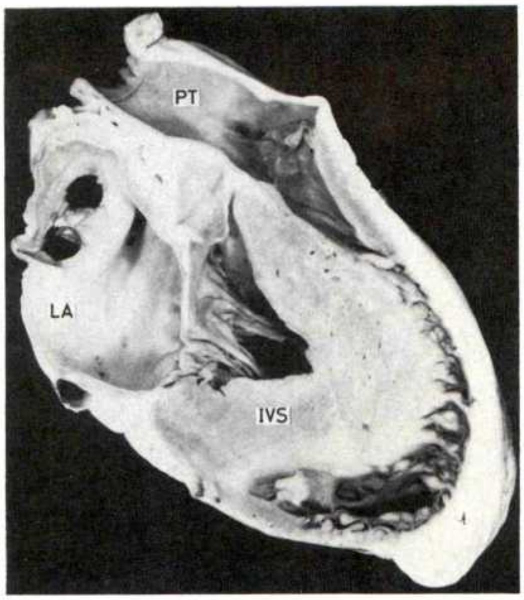

Figure 5 Anatomical section through the muscular interventricular septum (IVS) corresponding to section 4 in fig 1. The coaptation zone of the mitral valve is crossed near the posteromedial commissure. The section also shows the left coronary cusp and part of the adjacent sinus of Valsalva. LA, left atrium; PT, pulmonary trunk.

by further anticlockwise rotation of the probe from the position used for scanning the right ventricular outflow tract. The wedged position of the aortic root between the atrioventricular valvar junctions, and the curtain-shaped area of aortic-mitral valvar continuity could be assessed better by imaging in the transverse axis.

Further anticlockwise rotation of the probe directed the ultrasound beam towards the left side of the patient, showing the left ventricle in its long axis. Initially, such planes do not include the apex, thereby confirming that foreshortening of the left ventricle is possible on longitudinal imaging as it is on transverse imaging. With further anticlockwise rotation and slight leftward angulation of the transducer, however, the true apex of the left ventricle was shown (fig 7). The left atrium was traversed laterally, near the entry of the left pulmonary veins. Further rotation showed both the left atrial appendage in its long axis and the left upper pulmonary vein in the same cross section. The left upper pulmonary vein was seen cranioposteriorly to the junction of the left atrial appendage with the left atrium. Anterior and also cranial to the left atrial appendage, the left pulmonary artery was seen in its short axis.

Scanning beyond the left atrium towards the left hilum showed the left pulmonary veins and the left pulmonary artery in their short axes in front of the descending aorta (fig 8).

THORACIC AORTA

The proximal ascending aorta was well demonstrated in longitudinal echocardiographic planes (fig 9). Because the probe could be angled upwards from a site in the oesophagus just beneath the carina, the mid and upper parts of the ascending aorta could be imaged along a greater length than is possible with standard transverse imaging, which is limited by the interposition of the trachea between the oesophagus and the aorta. Nevertheless, even when transverse and longitudinal axes were used in combination, a short segment of the upper ascending aorta remained inaccessible from the oesophagus.

Conventional transoesophageal echocardiographic studies of the aortic arch in transverse planes produce long ellipsoid cross sections of the arch. As would be expected, therefore, scanning of the arch in longitudinal planes provided short axis or circular cross sections of the aorta (fig 10). A segment of one of the pulmonary arteries adjacent to the bifurcation of the pulmonary trunk was seen anteriorly and caudally. With the probe directed to the left or posteriorly from the oesophagus, longitudinal scans showed long segments of the descending aorta (fig 8), making the assessment of abnormalities of the thoracic aorta by biplane transoesophageal echocardiography faster and more detailed than is possible with single plane imaging.

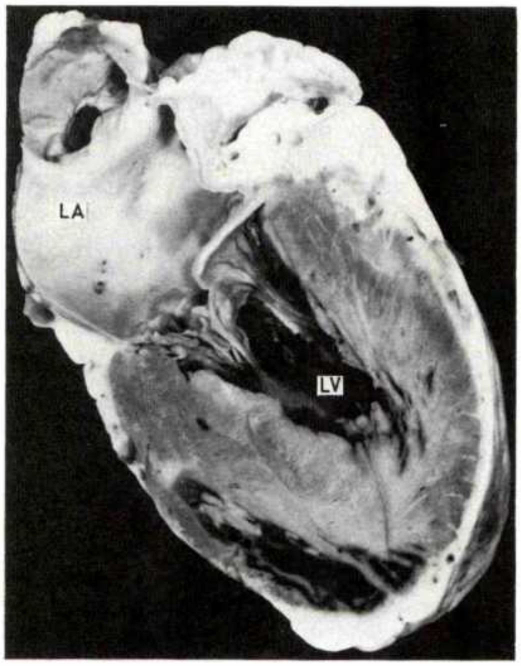

Figure 6 Anatomical section through the left ventricle corresponding to section 5 in fig 1. This shows the posterior muscular ventricular septum but not the true left ventricular apex. The mitral valve is sectioned in the middle third of the zone of coaptation. The site of drainage of both left pulmonary veins and the junction of the left atrial appendage with the atrial cavity are also seen. LA, left atrium; LV, left ventricle.

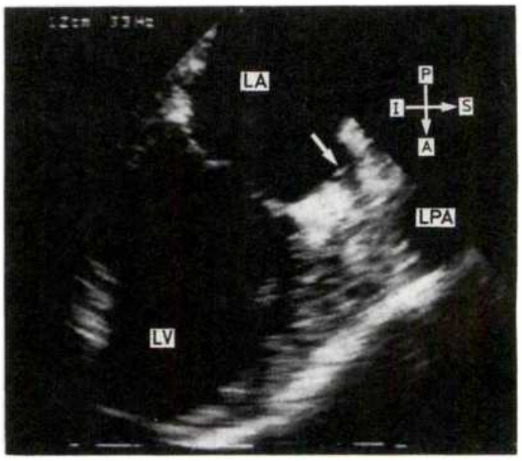

Figure 7 Longitudinal axis scan showing the left ventricle (LV) in its long axis and including the left ventricular apex. This view was obtained with slight left lateral angulation of the transducer. The zone of coaptation between the anterior (aortic) and posterior (mural) leaflets of the mitral valve is shown as is the junction (arrow) of the left atrial appendage with the left atrium (LA). The left pulmonary artery (LPA) is cut in its short axis.

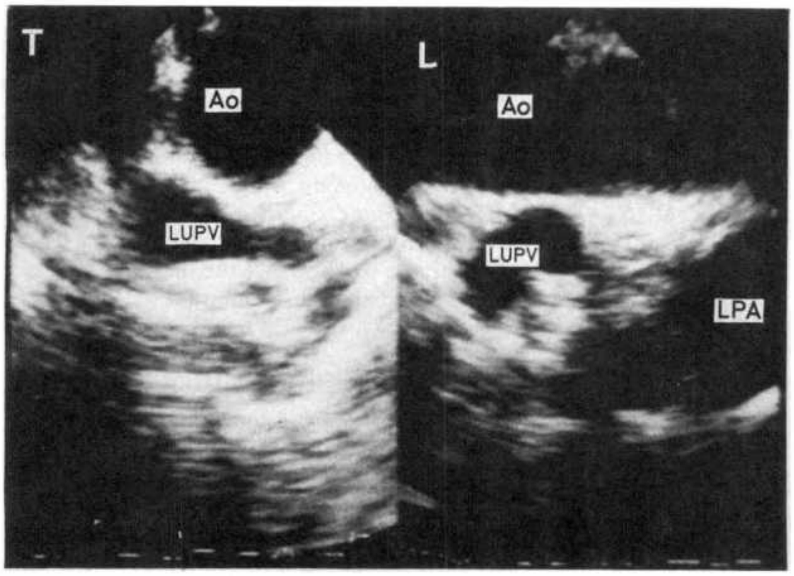

Figure 8 Transverse (T) and longitudinal (L) axial scans of the descending aorta (Ao) at the level of the left upper pulmonary vein (LUPV). Long segments of the anterior and posterior walls of the descending aorta are shown on the same longitudinal scan. Anteriorly the left pulmonary artery (LPA) and the left upper pulmonary vein are cut in short axis at their peripheral branching.

Discussion

Transoesophageal echocardiography is widely used for the investigation of adults with acquired heart disease. Current indications for transoesophageal studies include a suspected atrial abnormality,[10 11] atrioventricular valvar dysfunction,[12] endocarditis,[13 14] and abnormality of the aorta.[15 16] Although imaging in transverse axes provides excellent images and detailed diagnostic information, the range of scan planes that can be obtained is strictly limited, even when the steering facilities are fully used. Thus the introduction of additional imaging in the longitudinal axis, by Omoto and colleagues,[9] may further increase the diagnostic impact of transoesophageal echocardiography. We studied the anatomical details of these new longitudinal imaging planes. This study and our initial clinical experience suggest that the technique will be a valuable addition to standard transoesophageal imaging in the transverse axis in the assessment of specific aspects of both congenital and acquired heart disease.

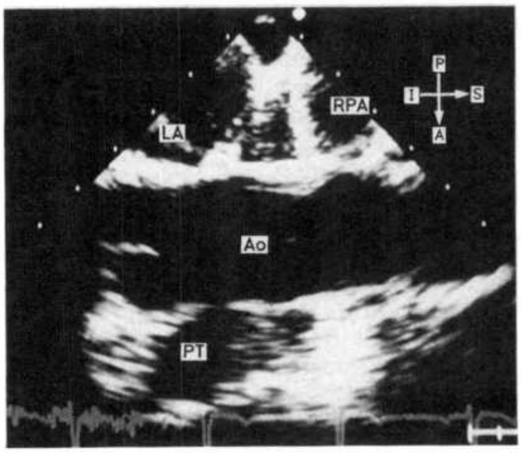

Figure 9 Longitudinal axis scan obtained when the tip of the probe was flexed upwards from a position behind the left atrium (LA). A long segment of the ascending aorta (Ao) is shown. Posteriorly the right pulmonary artery (RPA) and anteriorly (at the bottom of the image) a small segment of the proximal pulmonary trunk (PT) are also shown. The tricuspid valve and the right ventricle are not shown on this high longitudinal image, which corresponds to the upper half of the anatomical section in fig 3.

In congenital heart disease, imaging in the longitudinal axis showed the entire length of the right ventricular outflow tract; this was almost impossible when transverse axial planes were used on their own. In addition, the technique may enhance the assessment of overriding of the arterial valves over a ventricular septal defect. The planes were useful in determining the integrity of the interventricular septum and in showing the deviation and shape of its components and the relation of the ventricular chambers one to the other. Imaging in the longitudinal axis, therefore, may be expected to have considerable clinical impact on the echocardiographic assessment of complex congenital heart disease in adolescents and in adults with poor precordial windows.

In patients with acquired heart disease, early experience suggested that the technique will be most useful in assessing disease of the thoracic aorta,[17] such as dissection or aneurysm. The combination of imaging in the longitudinal and transverse planes now allows an almost complete echocardiographic assessment of the aorta between the aortic valve and the diaphragm. This should prove invaluable in the urgent diagnosis of patients with acute chest pain and suspected aortic dissection. However, even biplane transoesophageal imaging cannot display a small portion of the upper ascending aorta and the proximal arch, although this is considerably smaller than the area that is inaccessible to imaging in the transverse plane alone. Finally, colour flow mapping in the longitudinal axis will contribute towards a better understanding of the nature and shape of lesions of the aorta. For example, it may allow more rapid and accurate distinction between true and false lumens in aortic dissection.

Imaging in the longitudinal axis may also be of value in patients with diseases of the aortic root, such as infective endocarditis, and in those with prosthetic valve dysfunction, because it allows the examination of additional imaging planes. Although the technique cannot on its own provide a complete analysis of atrioventricular valvar shape, longitudinal imaging displays the anterosuperior and mural (inferior) leaflets of the tricuspid valve and it is useful for analysing coaptation over the medial half of the mitral valve. Thus it can complement the information that is obtained by precordial and transverse transoesophageal techniques. Biplane transoesophageal echocardiography may be used to obtain colour flow maps of regurgitant jets that can be analysed in orthogonal planes.

Scanning in the longitudinal axis from within the oesophagus has some limitations compared with transverse axial imaging. For example, it did not improve visualisation of the branches of the pulmonary trunk, which are always displayed either in oblique or short axes. In particular, no additional information is

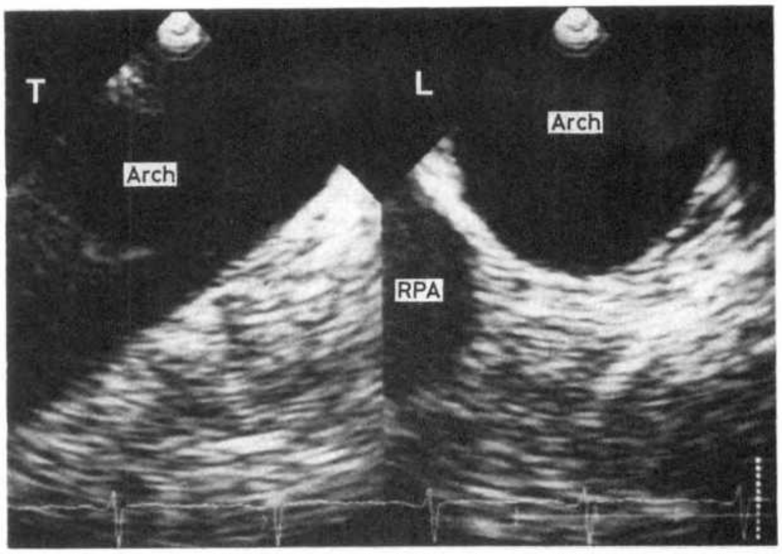

Figure 10 Transverse (T) and longitudinal (L) axis scans of the aortic arch. The aortic arch (Arch) is shown almost in its long axis on the transverse axis scan, whereas it is cut in short axis on the longitudinal scan. A segment of the proximal right pulmonary artery (RPA) is displayed inferiorly.

obtained on the course and shape of the left pulmonary artery, and transoesophageal imaging of this vessel remains difficult.

The longitudinal axial approach cannot contribute significantly to the haemodynamic evaluation of either congenital or acquired heart disease. The assessment of flow across the atrioventricular valves is similar with both approaches. Although the pulmonary trunk and the right ventricular outflow tract are much better displayed by longitudinal than by transverse imaging, pulsed Doppler interrogation in longitudinal planes is less rewarding, because the angle of incidence between the ultrasonic beam and the flow of blood in these structures always approaches 90°. Therefore, even when both planes are used in combination, the haemodynamic evaluation of cardiac lesions will require precordial ultrasound.

A final technical consideration that militates against the use of biplane transoesophageal probes for all routine transoesophageal studies is that the number of elements in each transducer is less than what is normally available with transducers designed for use in a single plane. Indeed, the high definition of standard transoesophageal imaging is a major advantage of the technique. At present, however, there is an inevitable compromise in biplane imaging because of the need to incorporate the electronic connections for two transducers within the shaft of one probe. These considerations account for the definition of the echocardiographic images presented in the present report which is less than what is now considered routine from single plane transoesophageal studies. In our opinion, biplane transoesophageal imaging should be performed only when prior clinical and echocardiographic assessment suggests that it may provide diagnostic images of unique value.

The addition of imaging in the longitudinal axis complements the standard transoesophageal echocardiographic technique. Some of the cross sections obtained are unique. A thorough understanding of the anatomical basis of transoesophageal imaging in the longitudinal axis will enhance the diagnostic impact of this important new technique.

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1 Schlüter M, Hanrath P. Transesophageal echocardiography: potential advantages and initial clinical results. *Practical Cardiology* 1983;**9**:149–80.
2 Gussenhoven EJ, Taams MA, Roelandt JRTC, *et al.* Transesophageal two dimensional echocardiography: its role in solving clinical problems. *J Am Coll Cardiol* 1986;**8**:975–79.
3 Abel MD, Nishimura RA, Callahan MJ, Rehder K, Ilstrup DM, Tajik AJ. Evaluation of intraoperative transoesophageal two-dimensional echocardiography. *Anesthesiology* 1987;**66**:64–8.
4 Schlüter H, Hinrichs A, Thier W, *et al.* Transoesophageal two-dimensional echocardiography: comparison of ultrasonic and anatomic sections. *Am J Cardiol* 1984; **53**:1173–8.
5 Seward JB, Khandheria BK, Oh JK, *et al.* Transesophageal echocardiography: technique, anatomic correlations, implementation, and clinical applications. *Mayo Clin Proc* 1988;**63**:649–80.
6 Gussenhoven EJ, van Herwerden LA, Roelandt J, *et al.* Detailed analysis of aortic valve endocarditis: comparison of precordial, esophageal and epicardial two-dimensional echocardiography with surgical findings. *J Cardiovasc Ultrasound* 1986;**14**:209–11.
7 Dahm M, Iversen S, Schmid FX, Drexler M, Erbel R, Oelert H. Intraoperative evaluation of reconstruction of the atrioventricular valves by transoesophageal echocardiography. *Thorac Cardiovasc Surg* 1987;**35**:140–2.
8 Poppele G, Kruger W, Langenstein B, Hanrath P. Membranöse subvalvuläre Aortenstenose. Nachweis mittels transthorakaler und transösophagealer 2-D-Dopplerechokardiographie. *Dtsch Med Wochenschr* 1988;**113**: 1224–8.
9 Omoto R, Kyo S, Matsumura M, *et al.* Bi-plane transesophageal Doppler echocardiography: its advantages and limitations. *Int J Card Imaging* 1989;**4**:57–8.
10 Hanrath P, Schlüter M, Langenstein BA, *et al.* Detection of ostium secundum atrial septal defects by transoesophageal cross-sectional echocardiography. *Br Heart J* 1983; **49**:350–8.
11 Aschenberg W, Schluter M, Kremer P, Schroder E, Siglow V, Bleifeld W. Transesophageal two-dimensional echocardiography for the detection of left atrial appendage thrombus. *J Am Coll Cardiol* 1986;**7**:163–6.
12 Taams MA, Gussenhoven EJ, Cahalan MK, *et al.* Transesophageal Doppler color flow imaging in the detection of native and Bjork-Shiley mitral valve regurgitation. *J Am Coll Cardiol* 1989;**13**:95–9.
13 Erbel R, Rohmann S, Drexler M, *et al.* Improved diagnostic value of echocardiography in patients with infective endocarditis by transesophageal approach. A prospective study. *Eur Heart J* 1988;**9**:43–53.
14 Taams MA, Gussenhoven EJ, Bos E, *et al.* Enhanced morphological diagnosis in infective endocarditis by transoesophageal echocardiography. *Br Heart J* 1990;**63**:109–13.
15 Erbel R, Mohr-Kahaly S, Rennoliet H, *et al.* Diagnosis of aortic dissection: the value of transesophageal echocardiography. *Thorac Cardiovasc Surg* 1987;**35**:126–33.
16 Taams MA, Gussenhoven WJ, Schippers LA, *et al.* The value of transoesophageal echocardiography for diagnosis of thoracic aorta pathology. *Eur Heart J* 1988;**9**:1308–16.
17 Shah PM, Omoto M, Adachi H, Matsumara M, Kyo S, Yokote Y. Diagnostic value of newly developed biplane transesophageal echocardiography in thoracic aortic aneurysms [Abstract]. *Circulation* 1989;**80**(suppl II):3.

Br Heart J 1990;**64**:289–90

CASE REPORT

Rash after treatment with anistreplase

Nigel Burrows, Robin Russell Jones

Abstract

A palpable purpura developed on the legs and lower abdomen of a woman of 54 five days after she was treated with anistreplase anisoylated plasminogen streptokinase activator complex (APSAC) for an acute myocardial infarction. Histological examination of a skin biopsy specimen taken 6 days after treatment showed leucocytoclastic vasculitis. The rash resolved within two weeks and there were no other complications.

An illness resembling serum sickness and presenting with pyrexia, peripheral oedema, arthritis/arthralgia, and rash can complicate treatment with streptokinase.[1–3] We report the development of a rash as the sole complication of treatment with anistreplase (anisoylated plasminogen streptokinase activator complex (APSAC)).

Case report

A 54 year old Asian woman presented with a 6 hour history of central chest pain radiating down the left arm. She had non-insulin dependent diabetes and hypertension that were well controlled by treatment with metformin (1 g twice a day), atenolol (100 mg once a day), and aspirin (100 mg daily). There had been no recent change to her medication. An electrocardiogram at presentation confirmed an acute myocardial infarction with considerable ST elevation in the inferior leads. She was treated with 30 units of anistreplase, without heparin, by slow intravenous injection.

She made an uneventful recovery until 5 days after anistreplase treatment when a palpable, purpuric rash developed mainly on the extensor aspect of her legs and extended to the lower trunk. Plasma urea, serum creatinine, a full blood count, and clotting studies were normal. Urine microscopy was negative. Tests for antinuclear factor, antibody to extractable nuclear antigen, rheumatoid factor, Australia antigen, and cryoglobulins were also negative. A biopsy specimen of lesional skin (figure), obtained on day six, showed a mixed perivascular inflammatory cell infiltrate, red cell extravasation, fibrinoid necrosis of the dermal blood vessels, and fragmentation of neutrophils (leucocytoclasia). Staining by direct immunofluorescence showed C3 and IgM around the blood vessels. These findings were consistent with an acute leucocytoclastic vasculitis.

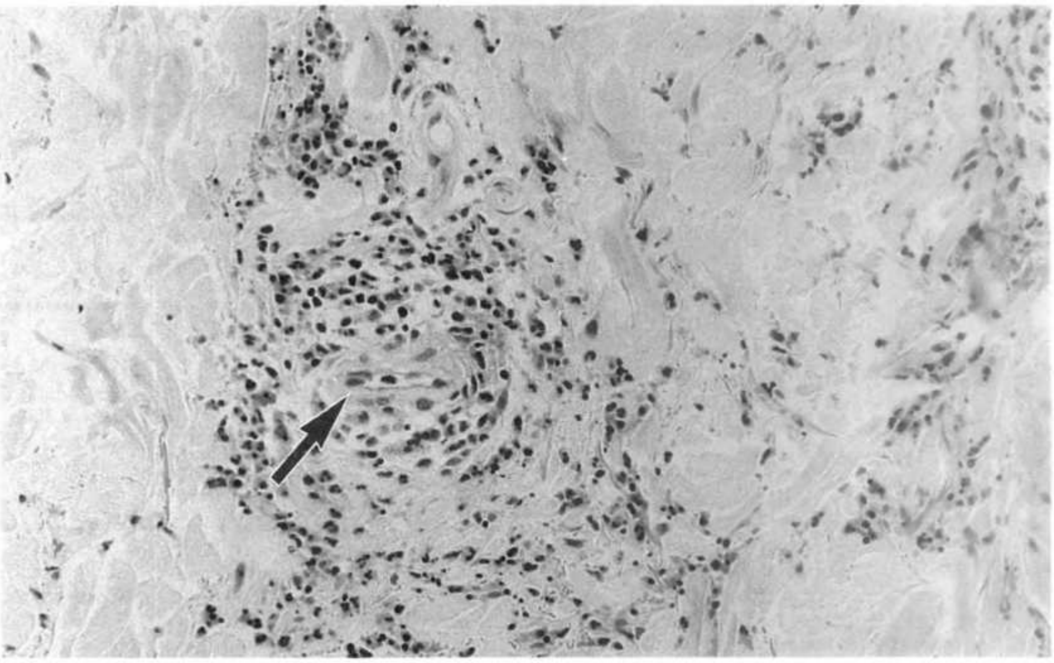

Figure A skin biopsy specimen taken 6 days after anistreplase. It shows leucocytoclastic vasculitis with a prominent number of neutrophils in the inflammatory infiltrate surrounding a venule (arrow).

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Discussion

The cutaneous manifestations of drug induced vasculitis are often associated with more serious systemic complications. In our patient, as with other reported cases,[4] the course was benign and the rash resolved within two weeks. A review of recent trials of anistreplase failed to mention purpuric rashes,[5] though this complication was found in 0·8% of patients receiving anistreplase.[6]

1 Alexopoulos D, Raine AEG, Cobbe SM Serum sickness complicating intravenous streptokinase therapy in acute myocardial infarction *Eur Heart J* 1984,5 1010–2

2 Noel J, Rosenbaum LH, Gangadharan V, Stewart J, Galens G Serum sickness-like illness and leukocytoclastic vasculitis following intracoronary arterial streptokinase *Am Heart J* 1987,113 395–7

3 Tott WG, Romano T, Benian GW, Gilula LA, Sherman LA Serum sickness following streptokinase therapy *AJR* 1982;138 143–4

4 Bucknall C, Darley C, Flax J, Vincent R, Chamberlain D. Vasculitis complicating treatment with intravenous anisoylated plasminogen streptokinase activator complex in acute myocardial infarction. *Br Heart J* 1988,59 9–11

5 Anonymous Alteplase and anistreplase in acute myocardial infarction *Drug Ther Bull* 1989;27.101–2.

6 Harrison I Anistreplase questions answered. *Br J Pharm Practice* 1989,11.361

BRITISH CARDIAC SOCIETY NEWSLETTER

Members will soon be receiving a mailing shot concerning the Glasgow meeting Preparations are now well under way. Accommodation has been reserved at a range of prices, but early booking is advisable The main conference hotel adjoins the conference centre Glasgow has worked hard to justify its claim to be the cultural centre of Europe. Members of the society may not (indeed should not .) have time to make an informed judgment on this claim during the course of the meeting, but we believe that the city will prove to be another popular venue. The format of the meeting will be very similar to that adopted in Torquay, with the first half day allocated to the working groups (Tuesday 30 April), followed by three days of the main meeting (Wednesday 1 May to Friday 3 May) On each day of the main meeting there will be plenary sessions in the morning and a named lecture in the evening The Young Research Workers Prize will be held on Thursday 2 May. the time for this has been increased so that each finalist will have 15 minutes for the presentation followed by 10 minutes for questions. The Nurses Day will also be on the Thursday and the Technicians Day has been arranged for Friday The closing date for abstracts is earlier this year than previously, and we have had to set this for 10 December.

The new training programme in cardiology continues to pose problems The Royal College of Physicians has given strong support to our need for protected registrar posts—essential if we are to plan training over six years in two blocks of three years. But other specialties feel the need for protected posts as well, a very reasonable viewpoint particularly for those with training needs similar to our own. The college therefore decided to make general recommendations to the Joint Planning Advisory Committee relating to registrar training, rather than supporting cardiology alone If the College recommendations are accepted, as surely they should be, the proposals for restructuring the registrar grade must be modified. It is as well to remember that the planned drastic cut back in registrar posts was to be introduced over a period of 10 years Some regions seem hell-bent on making the changes almost immediately. Less enthusiasm would be expected if expansion rather than contraction were being proposed

Members of the British Cardiac Society should know of the formation of a European Resuscitation Council. The idea was born of a frustrated attempt to form a working group on resuscitation within the European Society of Cardiology—rejected by the General Assembly in Dusseldorf. A group of cardiologists, with the United Kingdom well represented, met at the Vienna congress and decided that an organisation dedicated to resuscitation should be multidisciplinary if it were to be widely successful. The Resuscitation Council of the United Kingdom was a useful model The idea was well accepted, and plans moved ahead rapidly. An ad hoc meeting of interested individuals from several European countries took place in Antwerp in December 1988, and a provisional organisation was set up. The European Resuscitation Council was created formally in August 1989, and the first General Assembly of the Council was held in June 1990 The primary objective of the Council is "to preserve life by improving standards of resuscitation in Europe and to co-ordinate the activities of European organisations with a major interest in Cardiopulmonary Resuscitation (CPR)." The secondary objectives are "to produce guidelines and recommendations appropriate to Europe for the practice of cardiopulmonary and cerebral resuscitation; to update these guidelines in the light of critical reviews of the practice of cardiopulmonary resuscitation; to promote audit of resuscitation practice including standardisation of records of resuscitation attempts; to design standardised teaching programmes suitable for all trainees in Europe ranging from the lay public to the qualified physician; to promote and co-ordinate appropriate research; to organise relevant scientific meetings in Europe; and to promote political and public awareness of resuscitation requirements and practice in Europe " The societies that are represented on the council include: the European Society of Cardiology, the World Federation of Societies of Anaesthesiology (European Section), the European Academy of Anaesthesiology, the European Society of Intensive Care Medicine, and national societies of cardiology, anaesthesia, and intensive care from many European countries Informal contacts have already been made between the European Resuscitation Council and representatives from the American Heart Association National Emergency Cardiac Care Committee and the National Advanced Cardiac Life Support Subcommittee. An early meeting between the European Resuscitation Council and representatives of these two organisations is likely to take place in Norway at the end of the year to discuss uniform guidelines for reporting performance and outcome data in relation to cardiac arrest in hospital and out of hospital. Colleagues from Canada and Australia may also attend.

Harmonisation is the jargon word of the 90s, and the pursuit of uniformity threatens to become an end in itself. But the objectives here are sound, and progress is assured. The President represents the British Cardiac Society on the European Resuscitation Council He is a member of the Executive Committee and will attend the Norwegian meeting. The Officers of the European Resuscitation Council are. Chairman, Dr Peter Baskett (anaesthetist, UK); Vice Chairman, Dr Stig Holmberg (cardiologist, Sweden), Secretary, Professor Leo Bossaert (cardiologist, Belgium); Treasurer, Professor Daniel Scheidegger (anaesthetist, Switzerland). The Secretariat of the Council is located in Antwerp. The address is. European Resuscitation Council Secretariat, c/o Professor L Bossaert, University of Antwerp—UIA, Universiteitsplein 1, B2610 Antwerp, Belgium.

We end this letter with another request: that members of the society should consider using this page in the journal to put forward news and ideas, criticisms, and comments. We have heard it said that members have too little voice in the affairs of the society. We offer a platform, but where have the speakers gone?

DOUGLAS CHAMBERLAIN
President, British Cardiac Society
PAUL OLDERSHAW
Secretary, British Cardiac Society,
St Andrew's Place,
London NW1 4LB

NOTICES

British Cardiac Society

The Annual Meeting will take place at the Scottish Exhibition Centre, Glasgow on 30 April to 3 May 1991 The closing date for receipt of abstracts will be 10 December 1989

Clinical Autonomic Research Society

The Annual Meeting of the Clinical Autonomic Research Society will be held on 16 November 1990 at St Mary's Hospital Medical School, London. Inquiries to Dr David Jordan, Department of Physiology, Royal Free Hospital Medical School, Rowland Hill Street, London NW3 2PF. Telephone (071) 794 0500, extension 4304.

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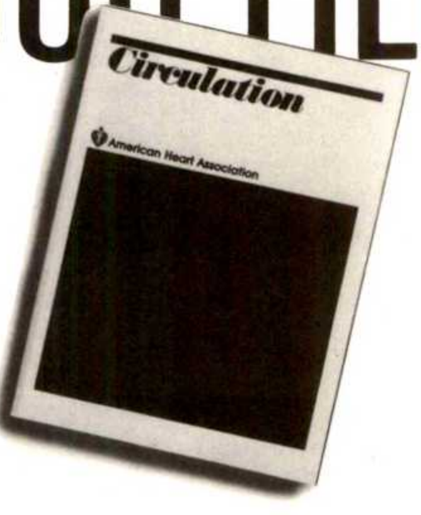

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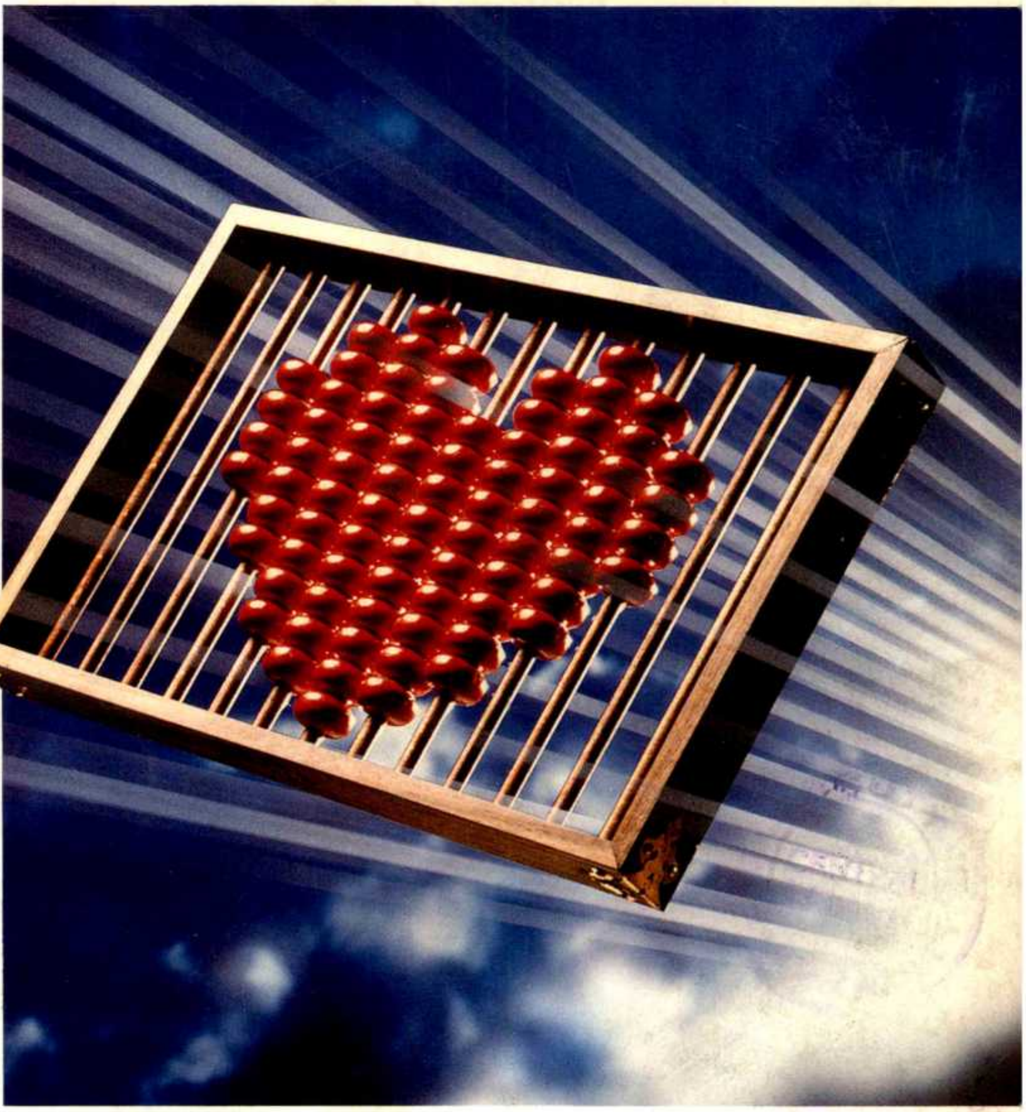

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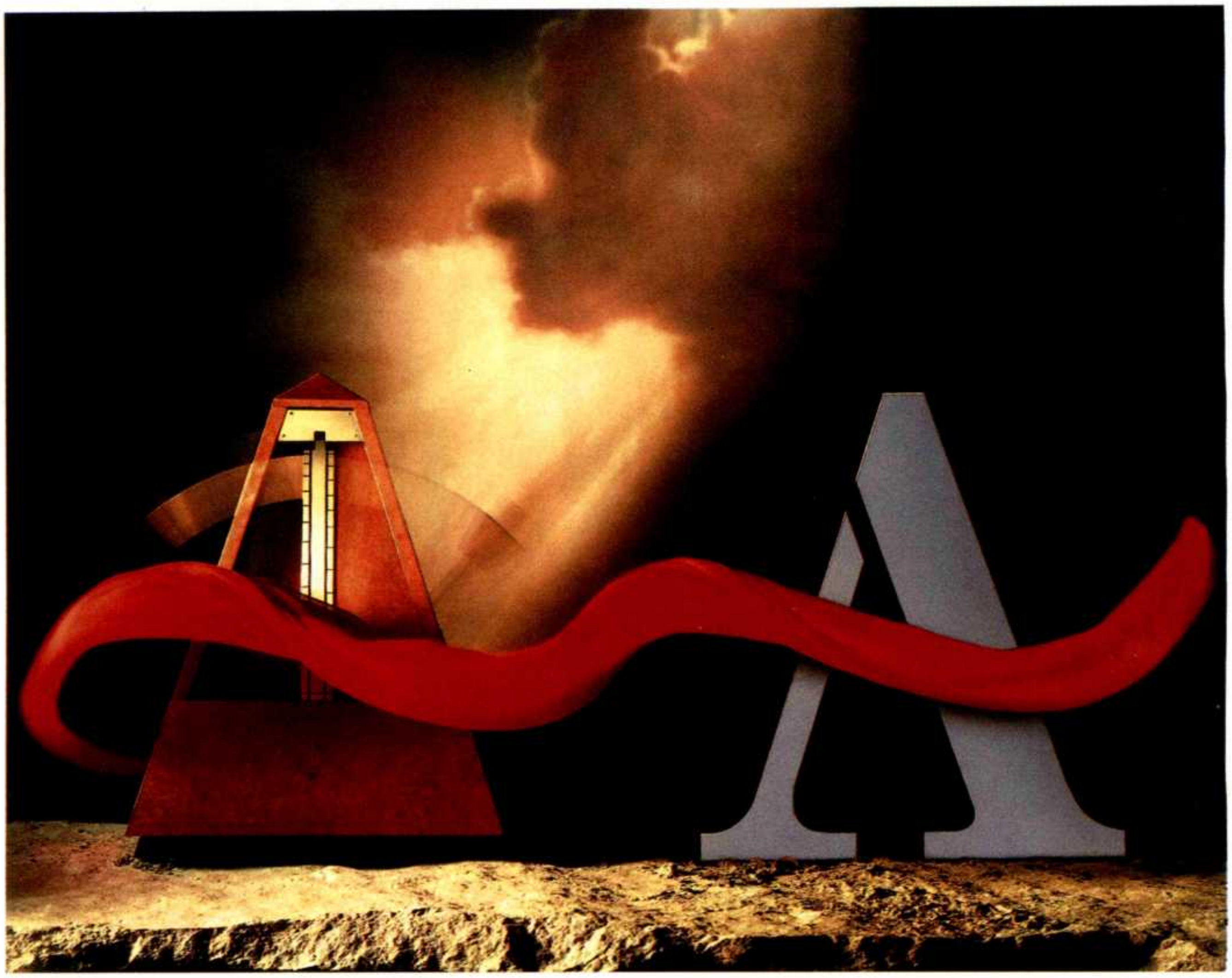

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Editorial

Should we get up in the morning? Observations on circadian variations in cardiac events

The recent fascination with circadian patterns in cardiovascular disease processes has led to a plethora of papers on the subject. But why do such variations occur and what does it all mean? In this article we analyse the findings of recent studies and discuss the clinical implications of circadian variations in cardiovascular disease processes.

Myocardial infarction, sudden cardiac death, and stroke

Several studies show a significant peak in the incidence of acute myocardial infarction in the morning waking hours.[1–4] Hjalmarson *et al*, in a study of over 4500 patients with acute myocardial infarction, reported a primary morning peak in events and a lesser evening peak (fig 1),[1] confirming the findings of Muller and colleagues.[2] In the ISAM (intravenous streptokinase in acute myocardial infarction) trial and the Physicians Health Study there was a significant morning peak in acute myocardial infarction.[3 4] Also Thompson and his colleagues found a primary peak in the morning and a lesser one at midnight for onset of chest pain.[5] Reports assessing the time of sudden cardiac death confirm the same morning peak in incidence.[6 7] This is not surprising because many sudden deaths result from acute myocardial infarction. The incidence of ischaemic stroke has also been shown to be highest in the morning.[8]

Why "thrombosis and death at dawn"?

To determine why these critical cardiac events cluster in the morning waking hours, we must look at the variables that predispose to such events. Myocardial ischaemia can now be assessed easily during daily routines by ambulatory ST segment monitoring, and in patients with coronary disease it has been amply demonstrated that there is a considerable increase in ischaemic activity (both silent and symptomatic) during the morning waking hours,[9 10] which may predispose to the end points of coronary disease. The variables that we seek to control by medical treatment in patients with coronary artery disease include heart rate, blood pressure, coronary blood flow, and the thrombotic state. It has now been shown that a surge in heart rate[11 12] and blood pressure[12 13] at this time coincides with a peak in catecholamine release.[14] These combined alterations increase myocardial oxygen demand, coronary and systemic vasoconstriction, and the risk of ventricular arrhythmia. The surge in blood pressure increases shear stresses at the sites of coronary stenoses which may lead to plaque fissuring with its resultant complications. Coronary blood flow is also significantly less in the morning than in the afternoon,[15] resulting in a reduction in myocardial oxygen supply. There is a peak in platelet stickiness in the morning[14 16] and a trough in the fibrinolytic state.[17 18] Thus the tendency to thrombosis is greatest at this time.

Should we stay in bed until after lunch?

Staying in bed in the morning is not likely to be cardioprotective; a recent study by Goldberg *et al*[19] tends to confirm this. They showed a peak incidence (23%) of onset of symptoms of acute myocardial infarction in the first hour after awakening rather than, less specifically, in the morning hours (fig 2).[19] Ridker *et al's* study also showed this association with awakening.[4] Rocco and colleagues showed that transient ischaemia is more common in the two hours after awakening.[9] The peak in platelet stickiness seems to relate not particularly to time but to getting up.[16] Though blood pressure begins to rise before waking the major surge results from the start of daily activities.[13] Finally, members

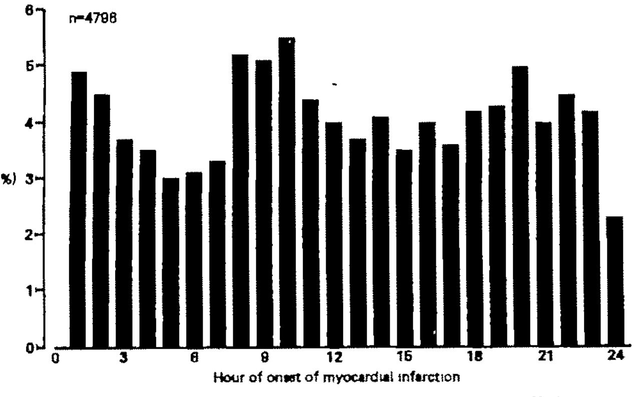

Figure 1 Distribution of hours of symptom onset of myocardial infarction (n = 4796) by six-hour intervals (reproduced with permission of Hjalmarson A, et al. Circulation 1989;80:267–75).

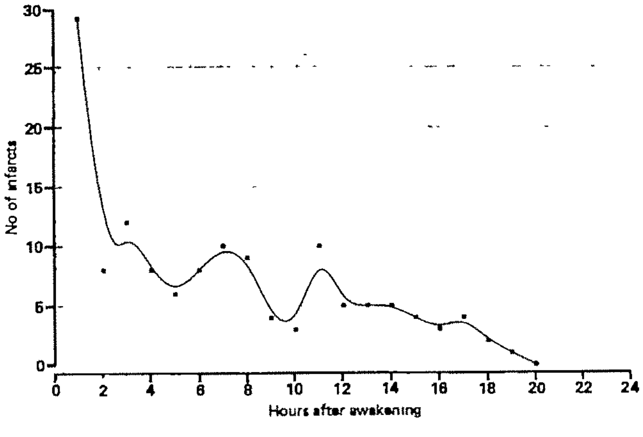

Figure 2 Time of onset of initial symptoms of acute myocardial infarction after awakening (reproduced with permission of Goldberg RJ, et al. Am J Cardiol 1990;66:140–4)

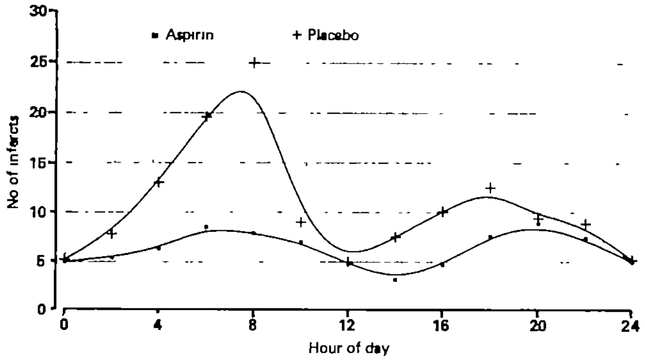

Figure 3 Estimated time and frequency of myocardial infarction onset among 11 034 subjects at risk in the aspirin group and 11 037 subjects at risk in the placebo group (reproduced with permission of Ridker PM, et al. Circulation 1990,82:897–902).

of a symphony orchestra who had an unusual temporal pattern of work showed significant alterations in the circadian pattern of heart rate,[20] which presumably reflects similar changes in catecholamine release and blood pressure. Because most people get up in the morning it is difficult to study circadian patterns in cardiac disease. If we all got up at noon the peak in cardiovascular events would probably simply be shifted to the afternoon. Thus the concept of "thrombosis and death at dawn" could be more aptly described as "thrombosis and death on arising". The potential cardiovascular benefits of not getting up at all would surely be far outweighed by a reduced quality of life and the complications of prolonged bed rest.

Can we modify these circadian patterns?

In theory, any pharmacological intervention that alters heart rate, blood pressure, coronary blood flow, or the thrombotic state favourably for the coronary patient should have its greatest beneficial effect in the morning waking hours. This has been confirmed in various studies. Muller *et al* noted that there was no morning peak in acute myocardial infarction in those receiving β blocking agents,[2] and this was confirmed in the ISAM trial[3] and in Hjalmarson's report.[1] Furthermore, β blockers eradicate the morning peak in ischaemia,[10,21] and in the Beta-Blocker Heart Attack Trial the incidence of sudden death was significantly reduced in the group receiving propranolol, with this beneficial effect being almost totally confined to the morning hours.[22] Calcium antagonists do not seem reliably to alter the circadian pattern of ischaemia[10] or acute myocardial infarction,[3] suggesting that alteration in coronary vasomotor tone is not the predominant precipitating factor in these morning events: indeed it has been clearly shown that those patients with extreme alteration in coronary vasomotor tone (coronary spasm) have a peak in ischaemic episodes at night.[23] A recent study of high doses of nifedipine, however, suggests that the morning surges in ischaemia can be prevented.[24]

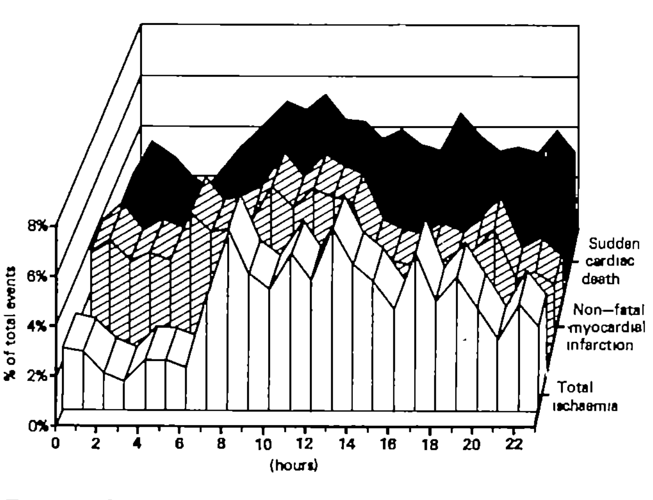

Figure 4 Circadian variation in transient myocardial ischaemia, non-fatal myocardial infarction, and sudden cardiac death (reproduced with permission of Mulcahy D, et al. Lancet 1988;ii:755–9)

Although Willich *et al* found no alteration in the "classical" circadian pattern of infarction in those receiving aspirin,[3] the recently published Physicians Health Study of over 22 000 subjects showed a significant reduction in the incidence of non-fatal myocardial infarction in those receiving aspirin, and showed that this beneficial effect resulted largely from a reduction in events in the morning waking hours, the reported time of peak platelet stickiness (fig 3).[4]

Clinical implications

Only one general fact has emerged from the study of circadian patterns in cardiovascular function: the time soon after awakening is a particularly dangerous one for the coronary patient (fig 4). This is not surprising because we know that all the variables that we seek to control and modify with medical or surgical intervention act against the patient with coronary disease primarily at this time. We now know that we can modify the circadian patterns of ischaemia and the end points of cardiac disease particularly with the use of β blockade, though whether this translates into an improved outlook for the patient is not clear. Aspirin modifies the morning peak in infarction and does improve patient outlook, suggesting a strong relation between platelet activity and acute myocardial infarction. The morning peak in "cardiovascular disease activity" and the alteration in circadian patterns in those with different temporal patterns of work emphasise the potential importance of 24 hour protection for the cardiac patient. Further study is required in patients with coronary artery disease and altered temporal patterns of work to establish whether the end points of coronary disease are related primarily to the sleep-wake period or to identifiable periods of increased activity or stress during daily life.

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1 Hjalmarson A, Gilpin EA, Nicod P, *et al* Differing circadian patterns of symptom onset in subgroups of patients with acute myocardial infarction. *Circulation* 1989;80:267–75.
2 Muller JE, Stone PH, Turi ZG, *et al* Circadian variation in the frequency of onset of acute myocardial infarction *N Engl J Med* 1985;313 1315–22
3 Willich SN, Linderer T, Wegscheider K, Leizorowicz A, Alamercery I, Schroder R. Increased morning incidence of myocardial infarction in the ISAM study: absence with prior beta-adrenergic blockade. *Circulation* 1989,80·853–8
4 Ridker PM, Manson JE, Buring JE, Muller JE, Hennekens CH. Circadian variation of acute myocardial infarction and the effect of low-dose aspirin in a randomized trial of physicians. *Circulation* 1990;82:897–902.
5 Thompson DR, Sutton TW, Jowett NI, Pohl JEF. Circadian variation in the frequency of onset of chest pain in acute myocardial infarction. *Br Heart J* 1991,65·177–8
6 Muller JE, Ludmer PL, Willich SN, *et al* Circadian variation in the frequency of sudden cardiac death. *Circulation* 1987,75:131–8.
7 Willich SN, Levy D, Rocco MB, Tofler GH, Stone PH, Muller JE. Circadian variation in the incidence of sudden cardiac death in the Framingham Heart Study population. *Am J Cardiol* 1987,60.801–6.
8 Marler JR, Price TR, Clark GL, *et al* Morning increase in onset of ischaemic stroke *Stroke* 1989,20·473–6
9 Rocco MB, Barry J, Campbell S, *et al* Circadian variation of transient myocardial ischemia in patients with coronary artery disease *Circulation* 1987,75 395–400

10 Mulcahy D, Keegan J, Cunningham D, *et al.* Circadian variation of total ischaemic burden and its alteration with anti-anginal agents. *Lancet* 1988;ii:755–9.

11 Northcote RJ, Canning GP, Ballantyne D. Electrocardiographic findings in male veteran endurance athletes *Br Heart J* 1989,61:155–60.

12 Millar-Craig MW, Bishop CN, Raftery EB. Circadian variation of blood pressure. *Lancet* 1978;i.797–9.

13 Furlan R, Guzzetti S, Crivellaro W, *et al* Continuous 24 hour assessment of the neural regulation of systemic arterial pressure and RR variabilities in ambulant subjects. *Circulation* 1990,81:537–47.

14 Tofler GH, Brezinski D, Schafer AI, *et al.* Concurrent morning increase in platelet aggregability and the risk of myocardial infarction and sudden death. *N Engl J Med* 1987,316:1514–8

15 Fujita M, Franklin D Diurnal changes in coronary blood flow in conscious dogs. *Circulation* 1987;76:488–91.

16 Brezinski DA, Tofler GH, Muller JE, *et al.* Morning increase in platelet aggregability. Association with assumption of the upright posture. *Circulation* 1988;78.35–40.

17 Andreotti F, Davies G, Hackett DR, *et al.* Major circadian fluctuations in fibrinolytic factors and possible relevance to time of onset of myocardial infarction, sudden cardiac death and stroke. *Am J Cardiol* 1988;62.635–7.

18 Angleton P, Chandler WL, Schmer G. Diurnal variation of tissue-type plasminogen activator and its rapid inhibitor (PAI-1) *Circulation* 1989;79 101–6.

19 Goldberg RJ, Brady P, Muller JE, *et al.* Time of onset of symptoms of acute myocardial infarction. *Am J Cardiol* 1990,66 140–4

20 Mulcahy D, Keegan J, Fingret A, *et al.* Circadian variation of heart rate is affected by environment: study of continuous electrocardiographic monitoring in members of a symphony orchestra. *Br Heart J* 1990;64.388–92

21 Cohn PF, Lawson WE. Effects of long-acting propranolol on AM and PM peaks in silent myocardial ischemia *Am J Cardiol* 1989;63 872–3

22 Peters RW, Muller JE, Goldstein S, Byington R, Friedman LM Propranolol and the morning increase in the frequency of sudden cardiac death (BHAT Study). *Am J Cardiol* 1989;63 1518–20

23 Nademanee K, Intarachot V, Josephson MA, Singh BN. Circadian variation in occurrence of transient overt and silent myocardial ischemia in chronic stable angina and comparison with Prinzmetal angina in men *Am J Cardiol* 1987;60:494–8.

24 Nesto RW, Phillips RT, Kett KG, McAuliffe LS, Roberts M, Hegarty P Effect of nifedipine on total ischemic activity and circadian distribution of myocardial ischemic episodes in angina pectoris. *Am J Cardiol* 1991,67:128–32.

Br Heart J 1991;65:302–10

REVIEW

Atherosclerosis: inhibition or regression as therapeutic possibilities

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Therapeutic modulation of the atherosclerotic process in human coronary arteries is now being attempted. A major aim of such attempts has been regression—that is, a diminution in the volume of atherosclerotic tissue. Many patients would, however, settle for stabilisation of their disease without further progression, and with a reduced risk of acute ischaemic events in the future. These may be more achievable aims.

Mechanisms of plaque growth

Atherosclerotic plaques grow by the accumulation of lipid and the production of connective tissue matrix proteins, such as collagen, by smooth muscle cells. Lipid accumulation within the intima is a complex process. Plasma low density lipoproteins (LDL) freely enter and leave the intima across the endothelial surface. The first morphological change in the initiation of atherosclerosis in humans and in all animal models[1 2] is the migration of monocytes through an intact endothelial surface into the intima; these monocytes subsequently take up LDL and become lipid filled macrophage foam cells within the intima. Monocytes do not, however, have a receptor which enables them to take up native LDL within the intima. This paradox was resolved when it was realised that modification of the LDL by acetylation or oxidation leads to avid uptake by macrophages via the alternative scavenger receptor.[3] Oxidation of LDL occurs within or adjacent to endothelial cells and after binding of LDL to proteoglycans, within the intima. Oxidised LDL acts as a chemoattractant for monocytes, which it immobilises in the intima. It also acts as an activating factor and is cytotoxic as well as being ingested to form cholesterol filled foam cells. Oxidised lipid has been shown within the intima both in experimental and human atherosclerosis.[4] The progression of plaques[5] is also associated with the accumulation of cholesteryl ester and cholesterol outside cells; this may be due either to release from dying foam cells or to direct extracellular conversion of LDL bound to the connective tissue matrix in the intima.[6] Smooth muscle cells will also take up low density lipoproteins but it is now apparent that most cells within the intima in which the cytoplasm is completely distended by lipid to form the classic foam cell are monocyte derived.[7]

Removal of cholesterol from the intima is mediated by high density lipoproteins (HDL), which also freely enter the arterial wall across the endothelium.[8] They are less avidly bound by the connective tissue matrix and, being smaller than LDL particles, can move freely within the intima. HDL has an affinity to bind unesterified cholesterol; subsequently, within the HDL/cholesterol complex the enzyme lecithin cholesterol acyl transferase (LCAT) re-esterifies the cholesterol and the whole complex passes back into the plasma. Cholesterol ester is now transferred, via the activity of cholesteryl ester transfer protein, to LDL and very low density lipoprotein (VLDL) particles which can be taken up by the liver cells. The initial step of creating unesterified cholesterol that is available for binding to HDL is complex and crucial to an understanding of how lipid can be removed from established plaques. Direct binding of unesterified cholesterol to HDL within the extracellular lipid component of the intima may occur but most current knowledge concerns the release of cholesterol from within macrophage foam cells. The reaction is mediated by the specific interaction of HDL with a macrophage surface receptor, the whole complex being internalised and then resecreted, having been enriched with cholesterol within the cell. There is a second pathway, in which conglomerates of cholesterol and phospholipid formed within lysosomes are extruded from the cell surface to be available for binding with HDL.[9 10] The rate and mechanisms by which crystalline cholesterol could be removed from the lipid core of human lesions are less certain.[11]

Smooth muscle proliferation and collagen synthesis are the other integral parts of plaque growth. This is, however, not always directly coupled to lipid accumulation; some plaques seem to be predominantly collagenous without a significant cholesterol component.

Within an individual coronary artery there can be plaques ranging from those with a negligible lipid content to those with over 50% of their volume occupied by lipid. It is not known whether these different forms of plaque evolve from each other or are initiated in different ways. Smooth muscle proliferation is driven by growth factors,[2] one potential source of which is the macrophage activated by lipid ingestion. Other sources include platelets, endothelial cells, smooth muscle cells, and the degradation products of fibrinogen.

The processes of smooth muscle proliferation and lipid accumulation might be expected to be linear with time. But angiographic studies show that the progression of coronary artery disease in humans is neither linear nor predictable.[12 13] New high grade lesions often appear in segments of artery that were normal at previous angiographic examination[14]; and it is impossible to foresee the site of a subsequent occlusion causing infarction. This unpredictable and episodic progress can be explained by the occurrence of thrombosis, as a complication of the basic atherosclerotic process, leading to intermittent plaque growth.[15 16]

It is important to appreciate that thrombosis occurring in an atheromatous plaque, often as a result of deep intimal tearing or fissuring, is very frequently clinically silent. Episodes of intraplaque thrombosis are an important mechanism of plaque growth[15] and it is only when significant intraluminal thrombosis occurs that there is a risk of acute myocardial ischaemia or infarction.

Methods of quantifying atherosclerosis

A major difficulty in any trial of antiatherogenic drugs in humans is quantification of the arterial lesions. The angiogram delineates the lumen which is at best an indirect guide to the state of the arterial wall. There are several reasons for this inexactitude. Plaques cause atrophy of the adjacent media; and when situated eccentrically the plaque shifts outward rather than bulging inward.[17] A consequence of this outward shift of the plaque, which comes to lie outside the original line of the artery, is that large plaques may not be associated with any stenosis, and can go totally undetected by angiography. In the early stages, diffuse atherosclerosis is also associated with a compensatory dilatation of the artery to preserve lumen size. This capacity to preserve the lumen size is not overcome until the area of the plaque exceeds 40% of the original cross sectional area of the artery.[18]

In the context of angiography "new" is not a relevant term because the threshold for detection of a plaque is high and not reached until it occupies 40% of the area of the cross section of the vessel. The appearance of a new lesion on angiography indicates a rapid growth phase and not the actual initiation of the plaque.

The conventional method of interpreting angiograms in clinical practice is to compare a test segment with an adjacent reference segment that is judged to be normal. But the reference segment may itself be diffusely narrowed (leading to an underestimate of the significance of the stenosis) or dilated (leading to an overestimate of the stenosis).[19]

Because the lumen is not necessarily circular different examinations can be compared only if the views of the arterial segment are in identical planes.[20] The crescentic and slit shaped lumens that often appear in pathology papers are artefacts of examining unperfused vessels, but even in vessels distended at high pressure D shaped lumens with flattening over a plaque do occur.[19]

Absolute lumen dimensions are less likely to be affected by these errors and are probably the ideal method in comparing angiograms.[21 22] This implies use of automated methods of quantification with an edge detection algorithm and computer assisted prediction of the outline of the normal vessel, exemplified by the Cardiovascular Angiographic Analysis System (CAAS) developed by Reiber *et al.*[23] The reproducibility of repeated measurements is better than that of visual assessments over a wide range of severity of stenosis.[24 25] The variability of absolute changes in vessel diameter is less than the calculated values of percentage diameter stenosis based on comparison with an adjacent reference segment of artery judged to be "normal".[26]

For all angiographic methods of measuring atherosclerosis it is essential that the vascular tone is identical during the two angiograms on which comparisons are being made. This proviso applies to both diffuse and focal disease. Atherosclerotic vessels have an abnormality of endothelial mediated vasodilatation[27] and any treatment that improves endothelial function or acts as a direct vasodilator can increase lumen size and give the spurious impression that this was caused by reduction in the mass of atherosclerotic tissue. Hyperlipidaemia can have a direct effect on endothelial function that is manifested far more widely than just within segments of coronary artery affected by atherosclerosis[28] and studies in rabbits showed that this was reversed by lowering plasma lipids.[29]

Clinical end points such as fatal and non-fatal myocardial infarction, unstable angina, or death from a cardiac cause are another way of assessing the response to treatment. They test the likelihood of episodes of major thrombosis, and thus the frequency of a plaque becoming unstable. As such they are measuring a different variable from the angiogram; it is to be hoped that antiatherogenic drugs will not only reduce inherent plaque growth but also reduce the risk of plaque instability—but this is not known for certain. Drugs with no action on the basic process of atherosclerosis itself but which reduce the thrombotic response to unstable plaques will also reduce fatal and non-fatal acute events in patients with coronary atherosclerosis.[30] There is, however, some evidence that aspirin not only reduces acute events but also the number of new coronary lesions that appear,[31] emphasising once again the important role of thrombosis in plaque growth.

In animal models of atherosclerosis more exact and direct methods of quantifying the extent of arterial disease can be used. The standard method is to measure the percentage of the intimal surface of the aorta that is occupied by lipid containing lesions after staining with lipid soluble dyes such as oil red O. The mean percentage intimal involvement can be compared in groups of animals that have been treated differently. Such models allow drugs to be evaluated either for inhibition of development or for the regression of atherosclerosis; but they give no indication of the risk of thrombosis because most experiments are short term.

Regression and inhibition in animal models of atherosclerosis

Atherosclerosis in animals is induced by hyperlipidaemia, either produced by high fat diets or by metabolic defects in lipid metabolism. The Watanabe rabbit[32] is deficient in the LDL receptor, and thus is analogous to human familial hypercholesterolaemia. The models can be criticised[33] for testing cholesterol accumulation in the aorta rather than the development of atherosclerosis per se, with grossly unphysiological levels of consumption of dietary fat compared with human consumption, and for being very short term. The morphology of the lesions is often dominated by the presence of intracellular lipid rather than the extracellular lipid cores characteristic of human advanced plaques. Monkey[1] and pig models[34] which produce a disease in the long term more analogous to human atherosclerosis, particularly if associated with hypertension,[35] are prohibitively expensive.

In animal models several drugs have been successful in retarding the development (drug given simultaneously with high lipid diet) or in causing regression (drug given after high lipid diet) of aortic lesions. They can be divided into those in which there is a significant lowering of plasma lipids and those which must have other mechanisms.

The models in which there was plasma lipid lowering include rabbits, pigs, dogs, chickens, pigeons, and monkeys.[36] Most of the studies compare the findings at necropsy in groups of animals treated differently, but in one the aorta was inspected at successive surgical explorations.[37] All these models showed that it is possible to reduce cholesterol content, lesion size, and the total number of lesions. Cholesterol is removed from the plaques far faster than collagen. In some models the amount of collagen within plaques actually increases, and heavily cross-linked collagen resistant to collagenolysis is deposited in the regression phase.[38, 39] In many animal models, unlike in humans, a high proportion of the cholesterol is contained within foam cells and is thus easily mobilised; in rhesus monkeys intra-arterial lipid was reduced within 4 weeks of the plasma lipid concentration returning to normal.[40] The mechanism by which lowering plasma lipids causes inhibition or regression of atherosclerosis is by reducing the amount of LDL entering the intima, which allows the natural clearance pathway via HDL to predominate.

With probucol inhibition of atherosclerosis was much greater than expected for the observed reduction in plasma lipid concentration.[41, 42] Carew and his colleagues showed that when plasma cholesterol decreased from a mean (SEM) of 761 (29) mg/dl to 618 (21) mg/dl with lovastatin the percentage area of the aorta occupied by plaques was reduced from 40·6 (5·1)% to 27·5 (4·6)%.[41] Probucol lowered plasma cholesterol (to 671 (20·7) mg/dl) less than lovastatin but reduced intimal involvement with atherosclerosis more (to 14·3 (2·1)%). The current view is that probucol prevents oxidation of LDL and therefore lipid uptake by macrophages within the intima to form foam cells.[43] Prevention of lipid oxidation may also reduce monocyte recruitment into the intima.

Calcium antagonists can also influence atherosclerosis. Most studies indicate inhibition of lesion development with a range of calcium antagonists including verapamil, diltiazem, amlodipine, and nifedipine.[44] A dose dependent inhibition occurs both in the amount of cholesterol deposited and in the number of plaques in nifedipine treated NZ rabbits on a high lipid diet.[45, 46] Results with nifedipine in the Watanabe rabbit, however, were more equivocal,[47] and at least in one high fat diet model showed no effect of nifedipine.[48] In another study calcium antagonists in general were shown to alter atherogenesis in the aorta but not in the coronary arteries.[49]

The mechanism by which calcium antagonists might inhibit the atherosclerotic process is far from certain but there is an embarrassing choice of possibilities. The role of calcium in atherogenesis may have been underestimated; Fleckenstein *et al* pointed out that by weight calcium is a major constituent of many plaques.[50] But Fleckenstein's original demonstration of the prophylactic value of calcium antagonists against toxic doses of vitamin D was in a model resembling Monckeberg's sclerosis rather than human coronary atherosclerosis.[51] While this beneficial effect in the vessel wall may be related to calcium channel inhibition, there must be an alternative mechanism for the ability of verapamil to inhibit cataract formation in the eyes of alloxan-diabetic rats.[52] This ability raises the possibility that some of the effects of calcium antagonists in inhibiting the formation of new atheromatous plaques could be the result of actions remote from an influence on the slow inward (calcium) channel of vascular smooth muscle cells.

There is increasing recognition that atherosclerotic plaques are the sites of intense inflammatory activity involving an interplay between T lymphocytes, monocytes, and smooth muscle cells signalled by the expresson of a range of cytokines and growth factors.[53, 54] Calcium antagonists might influence the transmission of these signals between cells. In vitro models of cell activation by platelet derived growth factor or interleukin 2 show that control of this step is mediated by synergistic interaction between triggering of the protein kinase C pathway and an increase in cytoplasmic free calcium.[55–57] If the concentration of intrinsic intacellular calcium is low one arm of the activation process becomes dependent upon exogenous calcium, which will no longer be available in the presence of a calcium channel blocking agent. In these circumstances the calcium antagonist is an inhibitor of cell activation.

Smooth muscle cells express voltage dependent (L type) calcium channels and in vivo experiments suggest that the calcium antagonists do inhibit smooth muscle proliferation and migration[45, 58–60] possibly through blocking the action of platelet derived growth factor.[57] In the Watanabe rabbit, drugs such as cortisone reduce the rate of plaque formation. This emphasises the "inflammatory" nature of the atherosclerotic process.[61]

Accumulation of extracellular lipid derived from dying foam cells[5 7] and necrosis, with the formation of an accellular lipid core within the plaque, is an integral part of progression in human atherosclerosis. Various lipid soluble factors can selectively accumulate within foam cells; the best characterised example of such a factor is 1,25-dihydroxycholecalciferol (vitamin D_3) which has a considerable calciotrophic effect leading to increased calcium mobilisation into the cell.[62] This increase may be toxic and lead to cell death that is manifest as plaque necrosis. Calcium antagonists might thus be potential vitamin D_3 antagonists capable of breaking a self perpetuating cytoxic cycle, and indeed they are known to block the arterial damage after external administration of the vitamin. Vitamin D_3 is, however, also produced within the macrophage[63] and this in situ production might continue at a lower level in the face of a calcium antagonist shifting what was a plaque with predominant necrosis to one which calcifies and becomes more stable.

Yet another possible cellular effect of calcium antagonists is that the intracellular enzymatic metabolic pathways may be sensitive to a calcium deficit and hence to a blocking agent. Such enzymes may be responsible for degradation of endogenous and exogenous protein and for intercellular lipid handling.[64] Hydrolysis of cholesterol ester within cultured smooth muscle cells is increased by calcium antagonists.[65 66] It is possible that if an atherogenic process continues in the presence of calcium antagonists there may be intrinsic changes in the nature of the intercellular lipids and hence in the behaviour of the foam cell. So far the effect has been studied in the smooth muscle cell whereas most foam cells are macrophages. The net uptake of lipid in vivo by macrophages has also been shown to be inhibited by calcium antagonists.[67 68]

Calcium antagonists may affect lipids within the intima at a simpler level than that of intracellular metabolism. Two dissimilar calcium antagonists, flunarizine and nimodipine, both reduced the permeability of the endothelium to LDL and thus would reduce lipid accumulation.[69] In a different context an article in this issue of the *British Heart Journal* reports that verapamil and nifedipine have antioxidant properties, which means that they may have an effect analagous to probucol in atherosclerosis.[70]

At present the mechanisms by which calcium antagonists influence atherogenesis are unknown. There is fragmentary evidence for an effect on cell interaction, on smooth muscle cell proliferation, on prevention of plaque necrosis, on modifying intracellular lipid metabolism, on reducing lipid influx, and that they prevent lipid oxidation.

It seems likely there will be further demonstrations that drugs including antioxidants and anti-inflammatory agents have local effects on cells in the microenvironment of the plaque and these will be shown to be effective in modifying atherosclerosis in simple animal models. Should this be so, they will be worthy of human studies.

Human studies of inhibition and regression of atherosclerosis

In human coronary arteries high grade stenotic lesions contain large amounts of both collagen and calcium in addition to lipid; the relative proportion of lipid varies considerably from plaque to plaque, and is often very low. If the lessons of the animal models are correct, and lipid is removed rapidly but collagen is removed very slowly, significant regression of lesions causing high grade obstruction in man is unlikely other than over a long time.[71] But the appearance of new lesions might be prevented, and lipid rich lesions might regress.

The propensity of plaques to become unstable and undergo fissuring and thrombosis is, however, related directly to the amount of extracellular lipid contained within the central core.[15 72 73] A reduction in the amount of lipid with only a modest reduction in overall plaque volume might be accompanied by an increase in plaque stability with a decrease both in episodic plaque growth and a reduction in the risk of acute ischaemic events. For this reason, data both on the angiographic severity and on the clinical event rate are needed to assess any intervention in atherosclerosis.

Despite all the reservations concerning the ability of the angiogram to measure wall disease it remains the only technique available. Computerised image analysis has improved the subjective bias inherent in any visual interpretation of angiograms and must be considered the optimum method. Subset analysis can be made of the progression of lesions of different severity in the initial angiogram.

Given the interplaque variation in the proportions of the volume of tissue made up of collagen, lipid, and calcium it is unlikely that all lesions in any patient could regress at the same rate. The usual method of interpreting quantitative angiograpic data is to take the mean change for all the angiographically detected lesions. This has statistical convenience for comparing study groups but the mean changes are often very small in haemodynamic terms and may be biased by a large change in a single lesion. An alternative method is to give a visual score for progression or regression to each patient based on the number of lesions in that individual showing a recognisable change in lumen size and ranging from +3 (change for better) through 0 (no change) to −3 (change for worse).

Since 1969 both angiography and the frequency of acute ischaemic events have been used as end points in trials of various methods to lower plasma lipids.

In 1976 a small study of 42 patients with femoral atherosclerosis showed that reduction in plasma lipids for one year was followed by angiographic improvement in six patients: on the other hand there was further luminal narrowing in 16 patients.[74] A randomised controlled trial of 24 subjects with hyperlipidaemia and intermittent claudication showed that after treatment with cholestyramine, nicotinic acid, and clofibrate the number of femoral arterial segments that showed progression of atherosclerosis was reduced from 17·3% in the control group to 6·9% in the treated group.[75]

Similar encouraging, though not startling, results were obtained by lowering plasma lipid concentrations in patients with coronary atherosclerosis. The National Heart Lung and Blood Institute study tested the effect of cholestyramine on coronary atherosclerosis in hyperlipidaemic individuals and reported cholesterol concentrations reduced by 26%.[76] Repeat angiography at five years in 59 treated patients and in 57 patients in a placebo group showed progression in 35% of those in the placebo group and in 25% in the test group; subclass analysis based on a range of angiographic variables suggested a favourable influence of treatment but clear statistical significance in the primary analysis was not achieved. A major difficulty in the study was that many individual patients showed both progression and regression at different sites within their coronary arteries.

Since these pioneer angiographic studies of regression other studies have been published. But there is no consensus on how to assess angiographic progression or regression in humans and trials of different methods both of deriving and analysing the measurements of stenoses are being reported. Direct comparison of these trials is therefore not easy.

In the Leiden Intervention Trial the plasma lipids were modified by diet alone; there was a modest reduction (mean (SD)) in total cholesterol (16·9 (1·4) mmol/l to 6·2 (1·3)) in 39 patients over two years without a control group.[77] In 307 lesions found on initial angiography, ranging from minor to high grade, quantification was by a computer assisted analysis using the CAAS system. The mean (SD) percentage stenosis of all 307 lesions increased from 44·1 (31·6)% to 48·6 (30 9)% over the two year period. Thus overall there was a significant progression of disease. Of the 39 patients, 21 showed an increase in the mean percentage stenosis and 18 showed no increase. Comparison of the total cholesterol and total/HDL cholesterol ratio in the two groups showed significant differences. In those with lesions that progressed total cholesterol was 6·5 (1·5) and total cholesterol/HDL ratio 7 1 (1·7) as against 5·8 (0·9) and 5·7 (1·2) respectively in those whose lesions did not progress. The results, while not showing regression, emphasised the role of raised total and LDL cholesterol and diminished HDL in influencing the progression of atherosclerosis.

In another study involving both a change in diet and lifestyle over a year LDL cholesterol was reduced by a mean of 37·4%.[78] One hundred and five lesions were detected by angiography in the 22 patients in the test group and 95 in the 19 patients of the control group. Quantification of the angiograms showed that there was an overall decrease (40·4 to 37·8%) in the mean degree of stenosis in the test group and an increase (42·7 to 46 1%) in the control group. The changes were similar for lesions causing more than and less than 50% stenosis. Four of the patients in the test group showed progression and 18 showed regression while in the control group 11 either showed no change or progression and eight showed regression.

In the Cholesterol Lowering Atherosclerosis Study (CLAS) 162 men undergoing coronary artery bypass grafting were randomised to treatment with colestipol and nicotinic acid or to placebo.[71 79] Angiographic assessment was visual and used both grades of progression and regression (+3 to −3) for lesions present at the initial angiogram and the appearances of new lesions. Repeat angiography at two years showed a reduction in the number of new lesions that appeared in both the native vessels and the grafts. In 80 treated patients 8 (10%) developed new lesions in the native coronary arteries compared with 18 (22%) of the 82 patients in the placebo group. The figures at four years continued the same trend with the difference in the frequency of new lesions being 14·3% *v* 10·4%. According to the overall scoring system, at two years 45% of the drug treated group were static compared with 36·6% of the placebo group; progression had occurred in 38·8% of the treated group and 59·8% of the placebo group. Regression at two years was noted in 16·2% of the treated group compared with 3·6% of the placebo group; by four years the figures were 17 9 and 6·4% respectively. Despite all of the difficulties inherent in an overall scoring system of the state of the coronary artery tree the different patterns of progression in the drug and placebo group seemed well established.

The Programme on the Surgical Control of Hyperlipidaemias (POSCH) study compared 421 patients treated by partial ileal bypass with 417 patients in a randomly allocated control group.[80] The entry criteria were survival after one infarct and a plasma cholesterol concentration of at least 5·69 mmol/l. A mean reduction in total cholesterol of 23·2%, a reduction of LDL cholesterol of 37 7%, and an increase of 4·3% in HDL were achieved. Mean follow up was 9·7 years with the angiograms being graded visually by two observers according to an eight point scale ranging from +3 to −3 from the CLAS study. Comparison of the angiograpic scores showed that 38·9% of patients in the treated group and 11 3% in the placebo group had remained static. In the treated group 54·8% showed progression but only 4·2% of these were graded as −3; in the placebo group 85% showed progression with 26·2% of them graded as −3. Regression was seen in 6·4% of the test and in 3·8% of the placebo group. The five patients with the best regression score (+3) all belonged to the placebo group—this result shows the unpredictability of atherosclerosis. The conclusion overall was that though there had been no regression, the rate of progression of atherosclerosis had been significantly slowed.

In the Familial Atherosclerosis Treatment Study (FATS) 146 individuals with angiographic evidence of coronary atherosclerosis and at least one segment of significant stenosis, a family history of coronary artery disease, and raised lipid concentrations were randomised to a control group, to lovastatin/colestipol, or to niacin/colestipol treatment.[81] In the two treatment groups LDL concentrations fell significantly and plasma HLD concentrations rose. Angiography was repeated 30 months later. Angiograms were visually assessed and selected lesions manually traced to allow accurate measurement of the stenosis and lumen diameter. Nine standard proximal segments of the three main coronary branches were identified and the worst stenosis in each segment was measured. The average percentage stenosis of the worst lesion in all segments was calculated and regression or progression was expressed as the change in this value between the two sets of angiograms. In a second end point, regression and progression were defined for each patient individually by a change of at least 10% stenosis in at least one of the lesions. In this particular study only five of the 120 patients who completed the study had a mixture of progressing and regressing lesions; the rest could all be clearly classified as no change, regression, or progression. The 52 patients in the placebo group showed a mean increase of stenosis of 2·1% (SD 3·9%) while the niacin/colestipol group (n = 48) showed a decrease of −9% (3·0%) and the lovastatin/colestipol group (n = 46) a decrease of −7% (5·3%). Forty six per cent of the placebo group progressed, 11% regressed, and 43% showed no change. The corresponding figures for the niacin/colestipol group were 25%, 39%, and 36% and for the lovastatin/colestipol group 21%, 32%, and 47%. One possible drawback in the study is that three of the four examples of striking angiographic regression illustrated could be regarded as acute unstable plaques in the initial study and the "regression" is caused by remodelling after organisation and lysis of thrombus.

Though these four recent angiographic studies of the effect of lipid lowering on the progression of coronary atherosclerosis used different selection criteria and methods to quantify regression and progression, some broad conclusions can be drawn. The studies that used some form of objective quantification of the stenosis and lumen diameter did show some evidence of regression overall but the changes were small in functional terms and achieved statistical significance by virtue of the power and precision of the studies. What is clear is that all the studies whether they use automated quantification or semi-quantified visual grading show evidence for a slowing in progression of the disease. It may be that more aggressive lipid lowering over longer periods will increase angiographic change but the evidence so far does not suggest that diseased vessels will miraculously return to normal or high grade lesions resolve and so avoid the need for angioplasty.

The FATS and POSCH studies were primarily concerned with the angiographic development of the coronary artery disease after lipid lowering but they also examined clinical events. In the large POSCH trial overall mortality caused by coronary heart disease was reduced (deaths overall 62 *v* 49, p = 0·16; coronary deaths 44 *v* 32, p = 0·11) but significance was achieved only if death due to coronary disease and non-fatal infarction were combined (125 *v* 82, p = 0·001).[80] In the far smaller FATS trial death caused by coronary disease and acute events such as unstable angina were considered together and were more common in the placebo group (10/52) than in the combined treatment groups (6/94, p = 0·01) representing a reduction in the incidence of clinical events of 73% but with wide confidence limits (23–90%).[81]

Evidence that calcium antagonists inhibited the development of atherosclerosis in animals prompted studies of their effect in humans in the International Nifedipine Trial on Antiatherosclerotic Therapy (INTACT).[82] The aim was to see whether nifedipine could inhibit the progression of angiographically demonstrated disease. The trial was a double blind randomised study of 425 patients, all aged less than 65 with mild disease and an ejection fraction of >0·40. Three hundred and forty eight patients were restudied at three years; 175 were in the placebo group and 173 had been treated with 80 mg of nifedipine daily. The angiograms were quantified by a computer analysis system (CAAS).

An increase in the degree of stenosis by more than 20% in established lesions was equally common in the two groups (9·4% of lesions on placebo, 11·7% on nifedipine). In the controls 4·1% of lesions regressed compared with 3·0% in the nifedipine group. Thus progression or regression of established lesions was not different. Two hundred and forty seven new lesions (including 19 new occlusions) appeared at sites where the angiogram had previously shown an apparently normal vessel. Of these new lesions, 103 occurred in treated patients and 144 in patients in the control group (p < 0·034). In terms of new lesions per patient the average was 0·59 *v* 0·82—a difference of 28%. These results thus suggested that nifedipine can slow the rate at which new atherosclerotic lesions appear on angiography. The study cannot, and never set out to, determine whether this modest reduction in the rate at which new lesions appeared was of any long term benefit to the individual patient. In the study cardiac events and mortality were, however, recorded, and correctly have been reported by the authors. There were eight deaths (three acute myocardial infarction, five sudden cardiac death) in the treated group and two sudden deaths in the controls.

The data from the INTACT study are supported by some other studies. In high risk patients nifidepine reduced the frequency of coronary vein bypass graft atheroma. In one study, one year after surgery 62 of 93 grafts in patients on nidefipine were disease free compared with 71 of 136 in the placebo group (67% *v* 52%, p < 0·04).[83] In a small study to compare angiographic progression over two years new lesions appeared in 10% of 39 patients on nifedipine, 34% of 36 patients on propranolol, and 29% of 38 patients on isosorbide dinitrate.[84] In a larger study of nicardipine 383 patients with coronary atherosclerosis that was demonstrable on angiography were randomised to treatment or placebo.[85] Quantification used the CAAS system. When all lesions were analysed irrespective of their initial severity an increase of 10% in diameter stenosis was found in 147 (12·7%) of 1153 lesions in the treated and 170 (14·5%) of 1170 lesions in the control group (NS). In 178 lesions of initially less than 20% of the diameter in the treated group 9·0% progressed compared with 16·3% of the 233 lesions in the control group ($p = 0{\cdot}038$). The results based on absolute changes in vessel diameter were similar. The result thus resembled that found in the INTACT trial. There was a positive relation between the inhibition of progression of mild lesions and the lowering of blood pressure. This suggests that control of hypertension might be the simplest explanation for the beneficial effect on lesion progression. In animal models, however, calcium antagonists do not lower blood pressure. So this simple explanation of the beneficial effect is unlikely to be the only one. The clinical event rate was similar in the two groups.

Larger, more complex, and expensive trials are needed to ascertain the influence of calcium antagonists and lipid lowering drugs on the subsequent risk of cardiac events. Reducing the number of new plaques that appear and preventing further progression should reduce the risk; geographic surveys of atherosclerosis in the human aorta and coronary arteries show that on a population basis the number of plaques, measured as a percentage involvement of the intima, predicts the frequency of acute myocardial infarction and deaths related to atherosclerosis.[86]

For all their technical complexity therapeutic trials using angiographic measurement of the development and progression of atherosclerotic lesions have considerable attraction. Because all the subjects in the trial have a measurable variable, differences between two treatment groups can be identified with relatively small numbers. Any result to which the word regression can be applied, albeit to a minor degree, has considerable emotive appeal. In contrast, trials using clinical events and mortality as end points need to be far larger and to last longer for sufficient adverse events to accumulate for comparison. The effects on events and mortality are, however, what we really need to know. However interesting they are in scientific terms, the angiographic studies are not yet a definite surrogate.

A review of all the randomised trials that have so far considered the effect of cholesterol reduction on total mortality[87] and coronary heart disease events confirms the original view[88] that if there is a significant increase in total cholesterol a 1% reduction produces a 2·5% reduction in event rate but a lesser effect on total mortality. There is no difference between primary and secondary trials in this regard and the basic pathology of the disease would not suggest there could be. The trials so far have been concerned with at best modest reductions in plasma lipids: the best recorded in the 19 trials analysed[87] is a mean of 17%. These statements are bedevilled by the confusion caused by talking of relative risk reduction when a clearer idea of the magnitude would be given by absolute values. Definitive recommendations for the control of plasma lipid concentrations must await the results of drug trials which produce a more considerable lowering of plasma lipids.

The angiographic studies published do not so far contain any information that should alter, one way or the other, the current therapeutic indications for calcium antagonists, but they are encouraging because they show that the early progresson of atherosclerotic plaques can be modified. Where they are likely to have symptomatic benefit by controlling angina or lowering blood pressure they may also have an additional antiatherogenic effect. The current evidence is an inadequate basis for recommending calcium antagonists outside the previously established indications, though they may ultimately turn out to have other properties as a useful by-product. Definitive recommendations on the role of calcium antagonists as antiatherogenic drugs must be based on the results of further trials designed to evaluate their effect on clinical events.

1 Faggiotto A, Ross R, Harker L. Studies of hypercholesterolaemia in the non-human primate. I changes that lead to fatty streak formation. *Arteriosclerosis* 1984;4·323–40.
2 Ross R. The pathogenesis of atherosclerosis—an update. *N Engl J Med* 1986,8:488–500
3 Steinberg D, Parthasarathy S, Carew T, Khoo J, Witzum J. Beyond cholesterol. Modifications of low-density lipoprotein that increases its atherogenicity. *N Engl J Med* 1989;320.915–24.
4 Yla-Herttuala S, Palinski W, Rosenfeld ME, *et al* Evidence for the presence of oxidatively modified low density lipoprotein in atherosclerotic lesions of rabbit and man. *J Clin Invest* 1989;84.1086–95.
5 Stary H. Evolution and progression of atherosclerotic lesions in coronary arteries of children and young adults. *Arteriosclerosis* 1989;9 1–19
6 Guyton J, Klemp K. The lipid rich core region of human atherosclerotic fibrous plaques: prevalence of small lipid droplets and vesicles by electron microscopy. *Am J Pathol* 1989,134:705–17.
7 Mitchinson MJ, Ball RY, Carpenter KLH, Enright JH Macrophages and ceroid in human atherosclerosis. *Eur Heart J* 1990;11(E):116–21.
8 Kovanen PT. Atheroma formation· defective control in the intimal round trip of cholesterol. *Eur Heart J* 1990;11(E) 238–46
9 Schmitz G, Bruning T, Williamson E, Nowicka G. The role of HDL in reverse cholesterol transport and its disturbances in Tangier disease and HDL deficiency with zanthomas. *Eur Heart J* 1990,11(E):197–211.
10 Slotte JP. HDL receptors and cholesterol efflux from parenchymal cells. *Eur Heart J* 1990;11(E)·212–7.
11 Small D. George Lyman Duff memorial lecture. Progression and regression of atherosclerotic lesions· insights from lipid physical biochemistry *Arteriosclerosis* 1988;8: 103–29
12 Bruschke A, Wijers T, Kolsters W, Landmann J. The anatomic evaluation of coronary artery disease demonstrated by coronary angiography in 256 nonoperated patients. *Circulation* 1981;63.527–40.
13 Rafflenbeul W, Nellessen U, Galvão P, Kreft M, Peters S, Lichtlen P. Progression and regression of coronary artery disease as assessed with sequential coronary angiography. *Z Kardiol* 1984;73(suppl II):33–40.
14 Ambrose J, Tannenbaum M, Alexopoulos D, *et al*. Angiographic progression of coronary artery disease and the development of myocardial infarction. *J Am Coll Cardiol* 1988;12 56–62.
15 Davies M. A macroscopic and microscopic view of coronary thrombi. *Circulation* 1990;82(suppl III):1138–46.
16 Ip J, Fuster V, Badimon L, Badimon J, Taubman M, Chesebro J Syndromes of accelerated atherosclerosis. role of vascular injury and smooth muscle cell proliferation. *J Am Coll Cardiol* 1990;15:1667–87.
17 Crawford T, Levene C. Medial thinning in atheroma. *J Pathol Bacteriol* 1953;66:19–23.
18 Glagov S, Weisenberd E, Zarins C, Stankunavicius R, Kolettis G. Compensatory enlargement of human atherosclerotic coronary arteries. *N Engl J Med* 1987;316: 1371–5.
19 Stiel G, Stiel L, Schofer J, Konath K, Mathey D. Impact of compensatory enlargement of atherosclerotic coronary

arteries on angiographic assessment of coronary artery disease. *Circulation* 1989;80:1603–9.

20 Thomas AC, Davies MJ, Dilly S, Dilly N, Franc F. Potential errors in the estimation of coronary arterial stenosis from clinical arteriography with reference to the shape of the coronary arterial lumen *Br Heart J* 1986;55:129–39.

21 Zijlstra F, van Ommeren J, Reiber J, Serruys P. Does quantitative assessment of coronary artery dimensions predict the physiological significance of coronary stenosis? *Circulation* 1987;75:1154–61.

22 Wijns W, Serruys P, Reiber J, *et al.* Quantitative angiography of the left anterior descending coronary artery: correlations with pressure gradient and exercise thallium scintigraphy. *Circulation* 1985;71:273–9.

23 Reiber JHC, Serruys PW, Kooijman CJ, *et al.* Assessment of short, medium and long term variations in arterial dimensions from computer assisted quantification of coronary arteriograms. *Circulation* 1985;71:280–8.

24 Detre KM, Kelsey SF, Passamani ER, *et al* Reliability of assessing change with sequential coronary arteriography. *Am Heart J* 1982;104:816–23.

25 Brown BG, Bolson EL, Dodge HT. Arteriographic assessment of coronary atherosclerosis. Review of current methods, their limitations and clinical applications. *Arteriosclerosis* 1982,2.1–15.

26 Ellis S, Sanders W, Goulet C, *et al.* Optimal detection of the progression of coronary artery disease. comparison of methods suitable for risk factor intervention trials. *Circulation* 1986;74 1235–42

27 Ludmer PL, Selwyn AP, Shook TL. Paradoxical vasoconstriction induced by acetylcholine in atherosclerotic coronary arteries. *N Engl J Med* 1986;315:1046–51.

28 Creager M, Cooke J, Mendelsohn M. Impaired vasodilation of forearm resistance vessels in hypercholesterolaemic humans *J Clin Invest* 1990;86:228–34.

29 Osborne J, Lento P, Siegfried M, Stahl G, Fusman B, Lefer A. Cardiovascular effects of acute hypercholesterolaemia in rabbits· reversal with lovastatin treatment. *J Clin Invest* 1989;83:465–73.

30 Hennekens CH, Buring JE, Sandercock P, Collins R, Peto R Aspirin and other antiplatelet agents in the second and primary prevention of cardiovascular disease. *Circulation* 1989;80:749–56.

31 Chesebro JH, Webster MWI, Smith HC, *et al* Antiplatelet therapy in coronary disease progression. reduced infarct and new lesion formation [Abstract]. *Circulation* 1989;80(suppl II) 266.

32 Kita T, Brown M, Watanabe Y, Goldstein J Deficiency of low density lipoprotein receptors of the WHHL rabbit, an animal mode of familial hypercholesterolemia *Proc Natl Acad Sci USA* 1981;78:2268–72.

33 Vesselinovitch D Animal models and the study of atherosclerosis. *Arch Pathol Lab Med* 1988;112:1011–7.

34 Fritz K, Augustyn J, Jarmolych J, Daoud A, Lee K. Regression of advanced atherosclerosis in swine. *Arch Pathol Lab Med* 1976;100·380–5

35 Prusty S, Kemper T, Moss M, Hollander W. Occurrence of stroke in a nonhuman primate model of cerebrovascular disease. *Stroke* 1988;19:84–90.

36 Blankenhorn D, Kramsch D. Reversal of atherosis and sclerosis. The two components of atherosclerosis. *Circulation* 1989;79:1–7.

37 DePalma R, Bellon E, Klein L, Koletsky S, Insull WJ Approaches to evaluating regression of experimental atherosclerosis. *Adv Exp Med Biol* 1977;82 459–70.

38 Armstrong M, Megan M Arterial fibrous proteins in cynomolgus monkeys after atherogenic and regression diets. *Circ Res* 1975;36:250–61.

39 Hollander G, Ozick H, Anselmo M, Sanders M, Lichstein E, Greengart A. Myocardial rupture following intracoronary thrombolysis therapy. *NY State J Med* 1984;84 129–31.

40 Stary H. Progression and regression of experimental atherosclerosis in rhesus monkeys. In· Goldsmith E, Morr-Hankowsky J, eds. *Medical primatology*. Basel: S Karger, 1972:356–7.

41 Carew T, Schwenke D, Steinberg D Antiatherogenic effect of probucol unrelated to its hypocholesterolemic effect: evidence that antioxidants in vivo can selectively inhibit low density lipoprotein degradation in macrophage-rich fatty streaks and slow the progression of atherosclerosis in the Watanabe heritable hyperlipidemic rabbit. *Proc Natl Acad Sci USA* 1987;84:7725–9

42 Kita T, Nagano Y, Yokode M, *et al.* Probucol prevents the progression of atherosclerosis in Watanabe heritable hyperlipidaemic rabbit, an animal model for familial hypercholesterlaemia. *Proc Natl Acad Sci USA* 1987;84:5928–31.

43 Parthasarathy S, Young SG, Witzum JL, Pittman RC, Steinberg D. Probuol inhibits oxidative modification of LDL. *J Clin Invest* 1986;77:641–4.

44 Henry P. Calcium antagonists as antiatherogenic agents. *Ann NY Acad Sci* 1988;522:411–9.

45 Henry P, Bentley K. Suppression of atherogenesis in cholesterol fed rabbits treated with nifedipine. *J Clin Invest* 1981;68:1366–9.

46 Nayler W, Dillon J, Panagiotopoulos S. Dihydropyridines and the ischemic myocardium. In: Lichtlen P, ed. *6th international Adalat symposium*. Amsterdam: Excerpta Medica, 1985:386–98.

47 Ishikawa Y, Watanabe N, Okamoto R, Watanabe Y, Fukuzaki H. Nifedipine suppressed atherosclerosis in cholesterol-fed rabbits but not in Watanabe heritable hyperlipidemic rabbits. *Atherosclerosis* 1987;64:79–80.

48 Stender S, Stender I, Nordestgaard B, Kjeldsen K. No effect of nifedipine on atherosclerosis in cholesterol-fed rabbits. *Arteriosclerosis* 1984;4:389–94.

49 Ginsberg R, Davis K, Bristow M, *et al.* Calcium antagonists suppress atherogenesis in aorta but not in the intramural coronary arteries of cholesterol-fed rabbits. *Lab Invest* 1983;49 154–8.

50 Fleckenstein A, Frey M, Thimm F, Fleckenstein-Grun G. Excessive mural calcium overload—a predominant causal factor in the development of stenosing coronary plaques in humans. *Cardiovascular Drugs and Therapy* 1990,4· 1005–14.

51 Janke J, Hein B, Pachinger O, Leder O, Fleckenstein A. Hummung arterioskelerotischer Gefassprozesse durch prophylaktische Behandlung mit MgCl$_2$, KCI und organischen Ca^{++}-Antagonisten (quantitative Studien mit Ca^{45} bei Ratten) In: Betz E, ed *Vascular smooth muscle Proceedings of a satellite symposium. XXV international congress of physiological sciences*. Berlin Springer-Verlag, 1972:71–2.

52 Fleckenstein A *Calcium antagonism in heart and smooth muscle· Experimental facts and therapeutic prospects* New York John Wiley & Sons, 1983 280–5.

53 Munro JM, Cotran RS. The pathologenesis of atherosclerosis. atherogenesis and inflammation. *Lab Invest* 1988,58:249–61.

54 Hansson GK, Jonasson L, Seifert PS, Stemme S. Immune mechanisms in atherosclerosis *Arteriosclerosis* 1989,9 567–78.

55 May WS, Sahyoun N, Wolf M, Cuatrecasas P. Role of intracellular calcium mobilisation in the regulation of protein kinase C-mediated membrane processes. *Nature* 1985;317 549–51

56 Nishizuka Y. Perspectives on the role of proteins kinase C in stimulus-response coupling. *JNCL* 1986,76 363–74

57 Block L, Emmons L, Vogt E, Sachinidis A, Vetter W, Hoppe J Ca^{2+} channel blockers inhibit the action of recombinant platelet-derived growth factor in vascular smooth muscle cells. *Proc Natl Acad Sci USA* 1989;86 2388–92

58 Nomoto A, Hirosumi J, Sekiguchi C, Mutoh S, Yamaguchi I, Aoki H Anti-atherogenic-activity of FRB4235 (Nilvadipine) a new potent calcium antagonist effect on cuff-induced intimal thickening of rabbit carotid artery. *Atherosclerosis* 1987;64 25–62.

59 Nillson J, Sjolund M, Palmberg L, Von Euler AM The calcium antagonist nifedipine inhibits arterial smooth muscle cell proliferation. *Atherosclerosis* 1985,58 109–22

60 Stein O, Halperin G, Stein Y. Long-term effects of verapamil on aortic smooth muscle cells cultured in the presence of hypercholesterolemic serum. *Arteriosclerosis* 1987,7 585–92.

61 Makheja AN, Bloom S, Muesing R, Simon T, Bailey JM Anti-inflammatory drugs in experimental atherosclerosis *Atherosclerosis* 1989,76·155–61

62 Rasmussen H, Matsumoto T, Fontaine O, Goodman DBP Role of changes in membrane lipid structures in the action of 1 25-di-hydroxyvitamin D$_3$. *Fed Proc* 1982,41·72.

63 Cohen MS, Gray TK. Phagocytic cells metabolize 25 hydroxyvitamin D$_3$ in vitro. *Proc Natl Acad Sci USA* 1984,81.931–4

64 Goldman R Dependence on Ca^{2+} of lipoprotein lipase stability. *J Leukoc Biol* 1990;48:193–9

65 Etingin OR, Hajjar DP. Nifedipine increases cholesteryl ester hydrolytic activity in lipid-laden rabbit arterial smooth muscle cells *J Clin Invest* 1985;75 1554–8

66 Etingin OR, Hajjar DP Calcium channel blockers enhance cholesteryl ester hydrolysis and decrease total cholesterol accumulation in human aortic tissue. *Cir Res* 1990,66: 185–90.

67 Daugherty A, Rateri DL, Schonfeld G, Sobel BE. Inhibition of cholesteryl ester deposition in macrophages by calcium entry blockers· an effect dissociable from calcium entry blockade. *Br J Pharmacol* 1987;91·113–8.

68 Schmitz G, Robenek H, Beuck M. Ca^{++} antagonists and ACAT inhibitors promote cholesterol efflux from macrophages by different mechanisms *Arteriosclerosis* 1988;8:46–56.

69 Strohschneider T, Betz E. Densitometric measurement of increased endothelial permeability in arteriosclerotic plaques and inhibition of permeability under the influence of two calcium antagonists *Atherosclerosis* 1989,75· 135–44

70 Noronha-Dutra AA, Steen-Dutra EM, Woolf N An antioxidant role for calcium antagonists in the prevention of adrenalin mediated myocardial and endothelial damage. *Br Heart J* 1991,65:322–5.

71 Blankenhorn D. Atherosclerosis regression in humans. In. Leaf A, Weber P, eds. *Atherosclerosis reviews*. New York· Raven Press, 1990:151–7.

72 Tracy R, Devaney K, Kissling G. Characteristics of the plaque under a coronary thrombus *Virchows Arch* [*A*] 1985;405·411–27.

73 Richardson P, Davies M, Born G. Influence of plaque configuration and stress distribution on fissuring of coronary atherosclerotic plaques. *Lancet* 1989;ii:941–4.

74 Blankenhorn DH. Angiographic evidence of atherosclerosis regression in man. In Schettler G, Goto Y, Hata Y, Klose G, eds. *Atherosclerosis IV*. Springer-Verlag, 1977.

75 Duffield R, Lewis B, Miller N, Jamieson C, Brunt J, Colchester A. Treatment of hyperlipidaemia retards progression of symptomatic femoral atherosclerosis: a randomised controlled trial. *Lancet* 1983,ii:639–42.

76 Brensike J, Levy R, Kelsey SF. Effects of therapy with cholesteryramine on progression of coronary arteriosclerosis: results of the NHLBI Type II coronary intervention study. *Circulation* 1984;69:313–24.

77 Arntzenius A, Kromhout D, Barth JD. Diet, lipoproteins and progression of coronary atherosclerosis. *N Engl J Med* 1985;312:805–11.

78 Ornish D, Brown SE, Scherwitz LW, *et al.* Can lifestyle changes reverse coronary heart disease. *Lancet*

1990;**336**:129–33.
79 Blankenhorn D, Nessim S, Johnson R, San Marco M, Azen A, Cashin-Hemphill L. Beneficial effects of combined colestipol-niacin therapy on coronary atherosclerosis and coronary venous bypass grafts. *JAMA* 1987;**257**:3233–40.
80 Buchwald H, Varco RL, Matts JP, *et al*. Effect of partial ileal bypass surgery on mortality and morbidity from coronary heart disease in patients with hypercholesterolemia. *N Engl J Med* 1990;**323**:946–55.
81 Brown G, Albers JJ, Fisher LD, *et al*. Regression of coronary artery disease as a result of intensive lipid-lowering therapy in men with high levels of apolipoprotein B. *N Engl J Med* 1990;**323**:1289–98.
82 Lichtlen P, Hugenholtz P, Rafflenbeul W, Hecker H, Jost S, Deckers J. Retardation of angiographic progression of coronary artery disease by nifedipine. *Lancet* 1990; **335**:1109–13.
83 Gottlieb S, Brinker J, Mellits E, *et al*. Effect of nifedipine on the development of coronary bypass graft stenoses in high risk patients. A randomized double blind, placebo-controlled trial [Abstract]. *Circulation* 1989;**80**(suppl II):A909.
84 Loaldi A, Polese A, Montorsi P, *et al*. Comparison of nifedipine, propanolol and isosorbide dinitrate on angiographic progression and regression of coronary arterial narrowings in angina pectoris. *Am J Cardiol* 1989;**64**:433–9.
85 Waters D, Lesperance J, Theroux P, *et al*. A controlled clinical trial to assess the effect of a calcium channel blocker on the progression of coronary atherosclerosis. *Circulation* 1990;**82**:1940–53.
86 Strong J, Solberg L, Restrepo C. Atherosclerosis in persons with coronary heart disease. *Lab Invest* 1968;**18**:527–37.
87 Holme I. An analysis of randomized trials evaluating the effect of cholesterol reduction on total mortality and coronary heart disease incidence. *Circulation* 1990;**82**:1916–24.
88 Lipids Research Clinics Program. The Lipid Research Clinics Coronary Primary Prevention Trial Results: II The relationship of reduction in incidence of coronary heart disease to cholesterol lowering. *JAMA* 1984;**251**:365–74.

PLANTS IN CARDIOLOGY

Coffea arabica L. From Bentley R, Trimen H. *Medicinal plants*. London: J and A Churchill, 1880:144.

Theobroma cacao L. From Kohler FE. *Medizinal-Pflanzen, Atlas* 1887; Band II: plate 183.

Camellia sinensis (L.) Kuntze. From Curtis W. *Botanical magazine* 1807;**25 and 26**: Tab 998.

Royal Botanic Gardens Kew.

Methyl xanthine diuretics

Caffeine, theobromine, and theophylline were first studied in 1886 and although they are now obsolete they were important before the discovery of the synthetic diuretics in 1951 and especially before organic mercurials were introduced in 1920. They act by depression of renal tubular reabsorption. Caffeine is only a weak diuretic. Theophylline was shown to be better than theobromine by H M Marvin in an excellent early clinical trial (*Journal of the American Medical Association* 1926;**87**: 2043–6). It was effective in two thirds of patients who were still oedematous after treatment with digitalis. Theophylline also has a direct stimulant effect on the myocardium which was demonstrated at cardiac catheterisation by McMichael and colleagues at Hammersmith Hospital (*Clinical Science* 1946–48;**6**:125–35) and shown by them to be greater than that of digoxin in hypertensive right heart failure.

Theophylline is found in the tea plant *Camellia sinensis* (Theaceae) a native of China and India but the amount, 0·1%, is small for clinical use so it has to be synthesised. Theobromine is present in the cocoa tree *Theobroma cacao* (Sterculiaceae) which comes from the tropical forests of South America. Caffeine is present in both tea and cocoa and in other traditional beverages. In Africa these are coffee *Coffea arabica* (Rubiaceae) and the cola nut *Sterculia acuminata* (Sterculiaceae). In South America the ancient drink maté is made from a species of holly *Ilex paraguariensis* (Aquifoliaceae) while yoco comes from a species of *Paullinia* (Sapindaceae). Thus the methyl xanthines come from six plant families in the Old and New World that have no obvious botanical similarities. As has so often happened with medicinal plants, their therapeutic value was discovered by chance.

Purgatives were often used to treat heart failure before the xanthine diuretics were introduced and several of them were plants—elaterium, senna, aloes, cascara, croton, rhubarb, and podophyllum. Presumably they produced their effect because of the coincidental sodium loss that accompanied diarrhoea.

Theophylline seems to be making an exciting therapeutic comeback. It is now used to control erythrocytosis in patients with renal transplants. It reduces erythropoietin production by adenosine antagonism (*New England Journal of Medicine* 1990;**323**:86–90.

A HOLLMAN

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Use: All grades of essential hypertension and renovascular hypertension. Congestive heart failure (adjunctive therapy).

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Elderly patients: No change from standard recommendations.

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Precautions: Assessment of renal function is recommended. Renal insufficiency; renovascular hypertension; surgery/anaesthesia; possibility of hypotension especially in ischaemic heart disease and cerebrovascular disease. Combination with antihypertensives may increase hypotensive effect. Sometimes increased blood urea and creatinine and/or cases of renal insufficiency if given with diuretics. Minimises thiazide-induced hypokalaemia and hyperuricaemia. Potassium supplements, potassium-sparing diuretics and potassium-containing salt substitutes not recommended. Indomethacin may reduce hypotensive effect. Possible reduced response in Afro-Caribbean patients. Use with caution in breastfeeding mothers. Do not use in aortic stenosis or outflow tract obstruction or cor pulmonale. Monitor lithium serum levels if lithium salts administered.

Side effects: Dizziness, headache, diarrhoea, fatigue, cough and nausea. Less frequently, rash and asthenia. Rarely, angioneurotic oedema and other hypersensitivity reactions; renal failure; symptomatic hypotension (especially if volume-depleted); severe hypotension (more likely if severe heart failure); palpitation; hyperkalaemia; increases in liver enzymes and serum bilirubin (usually reversible on discontinuation of 'Zestril') and impotence.

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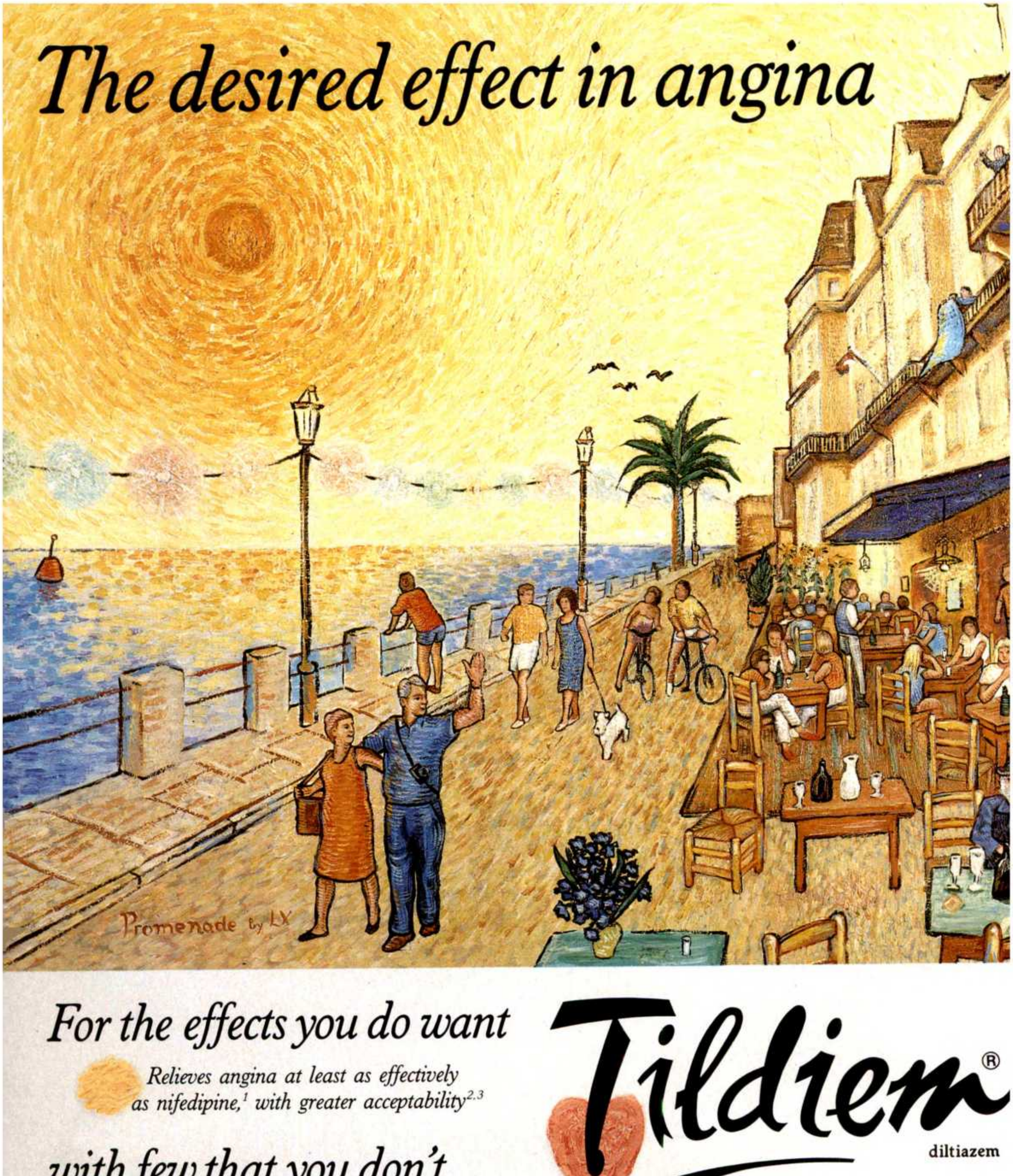
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TI: J5

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ORIGINAL ARTICLES

Determinants of successful transthoracic defibrillation and outcome in ventricular fibrillation

G W N Dalzell, A A J Adgey

Abstract

Objective—**To examine factors determining defibrillation success and outcome in patients with ventricular fibrillation.**

Design—**Observational prospective study of age, sex, transthoracic impedance, site of cardiac arrest, ventricular fibrillation duration and amplitude, primary or secondary ventricular fibrillation, aetiology, number of shocks to correct ventricular fibrillation, and drug treatment.**

Setting—**A teaching hospital and a mobile coronary care unit with a physician.**

Patients—**70 consecutive patients (50 male, 20 female) mean age 66·5 years.**

Interventions—**Before the first countershock was administered transthoracic impedance using a 30 kHz low amplitude AC current passed through 8 cm/12 cm self-adhesive defibrillator electrode pads applied in the anteroapical position was measured. The first two shocks were 200 J delivered energy (low energy) and further shocks of 360 J (high energy) were given if required.**

Main outcome measures—**Countershock success and outcome from ventricular fibrillation.**

Results and conclusions—**First shock success was significantly greater in in-hospital arrests (37/53) than in out-of-hospital arrests (5/17) and in those receiving antiarrhythmic treatment (13/15, 86·7%) *v* (27/51, 52·9%). Transthoracic impedance was similar in those who were successfully defibrillated with one or two 200 J shocks (98·7 (26) Ω) and those who required one or more 360 J shocks (91·4 (23) Ω). Success rates with two 200 J shocks were similar in those patients with "high" transthoracic impedance (that is, >115 Ω) and those with transthoracic impedance ($\leqslant 115$ Ω) (8/12 (67%) *v* 44/58 (76%)). Fine ventricular fibrillation was significantly more common in the patients with a transthoracic impedance of >95 Ω (41% (13/32)) than in those with a transthoracic impedance $\leqslant 95$ Ω (13% (5/38)). Death during arrest was significantly more common in patients who needed high energy shocks (14/18 (78%)) than in those who needed low energy shocks (16/52 (31%)). Multiple regression analysis identified ventricular fibrillation with an amplitude of $\geqslant 0{\cdot}5$ mV, age $\leqslant 70$ years, and arrests that needed $\leqslant$ two shocks for defibrillation, in rank order as independent predictors of survival to discharge.**

Transthoracic defibrillation remains a cornerstone of modern cardiological practice. Its more widespread application should improve the mortality from ischaemic heart disease, but further research into defibrillation techniques is essential to improve its efficacy. Many factors are thought to influence the success of ventricular defibrillation, but their relative importance is uncertain.[1]

Defibrillation occurs when an adequate intracardiac current depolarises a critical mass of myocardium.[2] The electrical circuit formed during defibrillation includes the impedance of the two electrode/electrolyte/tissue interfaces and that of the intervening tissues. The most variable component of the electrode-subject circuit is the impedance of the tissues of the thorax, which to a large extent influences the current that will flow through the myocardium.

The importance of transthoracic impedance as a determinant of intracardiac current flow[3] and the development of methods to predict the transthoracic impedance in advance of the shock[4] suggested that the assessment of its clinical role was relevant to present cardiological practice. Some previous studies of transthoracic impedance, however, have not assessed other factors that may influence defibrillation success and some combined results for different arrhythmias.[5 6] We have previously reported the influence of transthoracic impedance on the energy required for cardioversion of atrial fibrillation.[7] In the present prospective study we assessed the relative importance of all factors including transthoracic impedance in the determination of defibrillation and survival in patients with ventricular fibrillation.

Patients and methods

Data were collected on consecutive patients in whom cardiac arrest due to ventricular fibrillation occurred within or outside hospital. There were 70 consecutive cardiac arrests in which the initial rhythm was ventricular fibrillation in 50 male and 20 female patients (mean age 66·5 years (range 45–86)). In 52 acute myocardial infarction (a typical history of chest pain with an increase in cardiac enzymes

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to twice the normal concentration and serial electrocardiographic changes) was diagnosed. The site of infarction was anterior in 26, inferior in 16, other or undetermined in seven, and left bundle branch block in three. Four patients with documented ischaemic heart disease and no recent infarction developed ventricular fibrillation during the course of another illness: hypokalaemia, severe burns, pulmonary oedema, and after anaesthesia. Four patients had a history of proven ischaemic heart disease or suggestive chest pain before collapse and had sustained an out-of-hospital arrest and died before a definite diagnosis could be made. Of these 60 patients, 24 had had a previous myocardial infarction. Of the remaining 10, all of whom died during the initial arrest, the aetiology of the arrest was chronic airflow obstruction in one, pulmonary embolism in one, and no information was available in the other eight because they had no prior history of ischaemic heart disease and no necropsies were performed.

Thirty four patients sustained ventricular fibrillation in the hospital coronary care unit, 19 patients had ventricular fibrillation in another part of the hospital, and 17 had ventricular fibrillation out of hospital. Three of those who had ventricular fibrillation out of hospital developed ventricular fibrillation after the arrival of the mobile coronary care unit which was summoned because of chest pain.

Primary ventricular fibrillation was defined as ventricular fibrillation occurring in the absence of cardiac failure or hypotension, while secondary ventricular fibrillation occurred in the presence of one or both of these complications. Patients who collapsed with ventricular fibrillation outside hospital with "instantaneous" death who were previously well and who had no previous history of cardiac disease were classed as primary ventricular fibrillation.

The duration of arrhythmia before countershock was estimated by the physician managing the arrest. Coarse ventricular fibrillation was defined as having an amplitude $\geqslant 0{\cdot}5$ mV and fine ventricular fibrillation had an amplitude $< 0{\cdot}5$ mV. Previous treatment with antiarrhythmic drugs, digoxin, or β adrenergic blockers was recorded.

Self-adhesive electrocardiogram defibrillator pads (R2 Corporation) were used with a 12 cm diameter pad placed under the right clavicle adjacent to the right upper sternum and an 8 cm pad covering the cardiac apex. This anteroapical position was used for all patients with cardiac arrest. Standard defibrillators were modified to measure transthoracic impedance before delivery of the countershock while the defibrillator was being charged. A 30 kHz low amplitude (100 μA) current was passed through the chest via the electrode pads and the resultant voltage developed was proportional to the impedance. We have previously shown that this technique accurately predicts the actual transthoracic impedance for a defibrillatory countershock.[8] Three defibrillators were thus modified and their accuracy was checked daily against test resistances. One defibrillator was placed in the coronary care unit, and another on the cardiac arrest trolley, which was used throughout the hospital complex, and the third was used for the management of cardiac arrests out of hospital by a physician manned mobile coronary care ambulance. Transthoracic impedance results obtained before the first countershock were recorded for each cardiac arrest. Only the first episode of ventricular fibrillation during each cardiac arrest was included in the analysis of transthoracic impedance because transthoracic impedance is known to decrease with successive shocks.[9 10]

The effect of pad pressure on transthoracic impedance[11] was eliminated by pressing the adhesive pads firmly in position and not touching them during the delivery of countershock. It was possible to check the accuracy of pad position after cardiac arrest in the survivors because the edge of the electrode invariably left an erythematous ring on the patient's skin. One patient in whom the placement of electrode pads was deemed to have been suboptimal was excluded from the analysis.

Patients whose condition was initially stable when they were first seen by the mobile coronary care unit, but in whom ventricular fibrillation subsequently developed before arrival at the hospital, were included in the out-of-hospital group for analysis of data on site of arrest.

For attempted defibrillation the first shock was 200 J (delivered) followed by a second shock of 200 J if the first was unsuccessful. If two low energy shocks were unsuccessful we used shocks of 360 J. Defibrillation was defined as the electrical conversion of ventricular fibrillation to any other rhythm or to asystole. The success or failure of the first 200 J shock was noted as was the total number of shocks required to correct the first episode of ventricular fibrillation. The outcome was also noted: died during the arrest, survived the arrest but died later during the same hospital admission, or survived to be discharged.

Results

A single shock of 200 J was successful in 60% (42/70), and two 200 J shocks had a cumulative success rate of 74·3% (52/70). All patients were defibrillated at least once. Of the 70 patients, 30 (43%) died during the arrest, 13 (18·6%) survived but died later during their hospital admission, and 27 (38·6%) survived to be discharged from hospital.

AGE AND SEX

There was no difference in success of two 200 J shocks in patients aged 70 years or less (32/47, 68·1%) and those who were older than 70 (20/23 87·0%), $p > 0{\cdot}05$. Older patients, however, were less likely to survive the arrest itself and to reach discharge from hospital. A larger proportion of the younger patients (44·7% (21/47)) survived to discharge than of those over 70 years (26% (6/23)) ($p = 0{\cdot}04$). First shocks were equally successful in men and women (men 30/50, 60% *v* women 12/20, 60%). There was no significant difference in transthoracic impedance between men (mean (SD) 91·8

(21) Ω) and women (96·7 (SD) 29 Ω) (p > 0·05).

TRANSTHORACIC IMPEDANCE

The mean (SD) transthoracic impedance of this group was 93·3 (22) Ω (range 38–137). Univariate analysis showed that the first shock or two low energy shocks were as successful in those with an initial transthoracic impedance of >95 Ω as in those with transthoracic impedance of ⩽95 Ω (fig 1). Nor was there any difference between those with a transthoracic impedance >115 Ω (mean (1SD)) and ⩽115 Ω (fig 1). The mean transthoracic impedance for those who were successfully defibrillated with one or two 200 J shocks was 98·7 (26) Ω, compared with 91·4 (23) for those who required one or more shocks of 360 J for defibrillation (p > 0·05). But outcome was not as good in patients with a transthoracic impedance of >115 Ω. Only 8·3% (1/12) of them survived to leave hospital, compared with 44·8% (26/58) in the group with a transthoracic impedance ⩽115 Ω (p < 0·05). There was a significant relation between transthoracic impedance and ventricular fibrillation amplitude. Of the patients with a transthoracic impedance >95 Ω, 41% (13/32) had fine ventricular fibrillation compared with only 13% (5/38) of those with a transthoracic impedance ⩽95 Ω (p = 0·02). There was no significant difference in transthoracic impedance between those with out-of-hospital ventricular fibrillation and those with ventricular fibrillation occurring within hospital.

SITE OF CARDIAC ARREST, DURATION OF VENTRICULAR FIBRILLATION, AND AMPLITUDE OF VENTRICULAR FIBRILLATION

Ventricular fibrillation occurring in hospital was associated with a significantly higher first shock success rate than ventricular fibrillation occurring outside hospital (37/53 (69·8%) *v* 5/17 (29·4%) p = 0·007). The location at which the arrest occurred also determined survival. The death rate was lower and the discharge rate higher for arrests that occurred in the coronary care unit group than for arrests that happened elsewhere in the hospital, and survival was poorest for arrests out of hospital (fig 2).

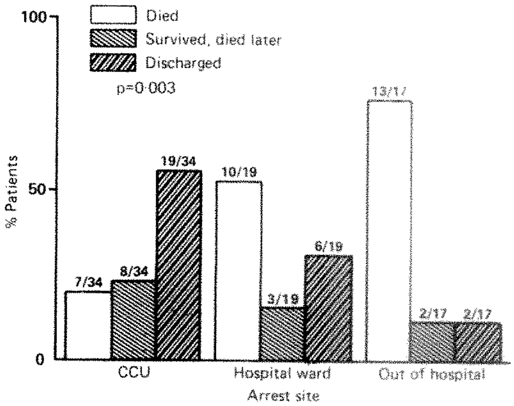

Figure 2 Arrest site and outcome of ventricular fibrillation. Outcome for patients with ventricular fibrillation out of hospital was significantly worse than for those who developed ventricular fibrillation within the coronary care unit (CCU) or another ward within the hospital.

Ventricular fibrillation lasted >3 minutes in 19/70 patients and ⩽3 minutes in the remaining 51. The duration of ventricular fibrillation was not significantly associated with success of a 200 J shock, but was significantly associated with outcome. Only 2/19 (10·5%) patients in whom ventricular fibrillation lasted >3 minutes survived to discharge, compared with 25/51 (49%) in whom it lasted ⩽3 minutes (p < 0·001). Ventricular fibrillation lasting more than three minutes was more likely to be fine amplitude (11/19, 57·9%) than ventricular fibrillation lasting ⩽ three minutes (7/51, 13·7%) (p < 0·001).

A single shock was successful in 61·5% (32/52) of patients with coarse ventricular fibrillation and 55·6% (10/18) in those with fine ventricular fibrillation (p > 0·05). Similarly, two 200 J shocks had a cumulative success rate of 76·9% (40/52) in patients with coarse ventricular fibrillation compared with 66·7% (12/18) in those with fine ventricular fibrillation (p > 0·05). Only two patients with fine ventricular fibrillation survived the arrest, and none survived to be discharged from hospital.

PRIMARY AND SECONDARY VENTRICULAR FIBRILLATION

Secondary ventricular fibrillation occurred in 18 patients; it was not more difficult to defibrillate than primary ventricular fibrillation. The first shock success rates (13/18 (72·2%) *v* 29/52 (55·8%) and cumulative success of two 200 J shocks (14/18 (77·8%) *v* 38/52 (73·1%)) were similar in secondary and primary ventricular fibrillation (p > 0·05).

AETIOLOGY OF VENTRICULAR FIBRILLATION

Ventricular fibrillation was caused by acute myocardial infarction in 74·3% of patients (52/70). This group had a cumulative defibrillation success rate with two 200 J shocks of 75·0% (39/52) that was similar (72·2% (13/18)) to that in other patients (p > 0·05). None the less, survival was significantly better for this subgroup, both for survival from the arrest initially (35/52 (67·3%) *v* 5/18 (27·8%)) and for discharge from hospital (24/52 (46·2%)) *v* 3/18 (16·7%)), p = 0·01.

NUMBER OF SHOCKS AND OUTCOME

The total number of shocks required to correct

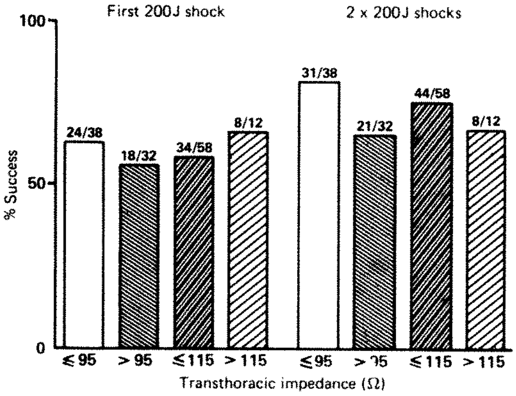

***Figure 1** Success of first 200 J shock and two 200 J shocks in patients with transthoracic impedance >95 Ω and ⩽95 Ω, and >115 Ω and ⩽115 Ω. There was no significant difference in shock success at any of the transthoracic impedance levels.*

ventricular fibrillation was related to outcome. Of those requiring low energy shocks (one or two 200 J shocks to correct ventricular fibrillation) 46·2% (24/52) survived to discharge compared with only 16·7% (3/18) of those requiring high energy—that is, >2 shocks ($p = 0·05$). A significantly higher proportion of patients in the high energy group died during the arrest (14/18 (77·8%) *v* 16/52 (30·8%) $p = 0·002$).

Those who received more than five shocks had a less favourable outcome. None of the eight patients given more than five shocks survived the arrest whereas 64·5% (40/62) of those given five or fewer than five shocks survived ($p = 0·002$).

DRUG TREATMENT

There were data on digoxin treatment for 67 patients, and on antiarrhythmic agents and β adrenergic blockers for 66 patients. Eighteen patients were not taking any of these drugs, four were taking β blockers only, one digoxin only, and one antiarrhythmic agents only. The remaining 42 patients were taking various combinations of drugs. Individual antiarrhythmic agents were not identified because the small numbers of each would have rendered analysis difficult. Most of the 15 patients who were taking antiarrhythmic agents before ventricular fibrillation developed were treated with either lignocaine or mexiletine. One patient had been receiving intravenous bretylium tosylate and four amiodarone. Twenty four patients were taking digoxin and seven β adrenergic blocking agents. Previous treatment with digoxin or β adrenergic blocking agents had no significant effect on shock success or outcome. Antiarrhythmic treatment was associated with improved first shock success rates (13/15 (86·7%) *v* 27/51 (52·9%) $p = 0·04$).

MULTIPLE REGRESSION ANALYSIS

A multiple regression analysis was performed to assess the predictive value of the following factors in determining first shock success: age, sex, transthoracic impedance, arrest site, duration of ventricular fibrillation, ventricular fibrillation amplitude, type of ventricular fibrillation (primary or secondary), aetiology of ventricular fibrillation, and drug treatment. Multiple regression identified arrest site in hospital as the most important predictor of first shock success. Treatment with antiarrhythmic agents was identified as the second most important predictive factor. No other variables contributed significantly.

For outcome from ventricular fibrillation, a second multiple regression analysis was performed. The same factors plus the total number of shocks required for defibrillation were entered. The factors of greatest significance in predicting discharge from hospital in rank order of importance were ventricular fibrillation amplitude $\geqslant 0·5$ mV, age $\leqslant 70$ years, and $\leqslant 2$ shocks to correct ventricular fibrillation.

Discussion

In this group of patients with ventricular fibrillation, defibrillation success with 200 J shocks was not related to transthoracic impedance. Multiple regression analysis did not select transthoracic impedance as an important predictor of first shock success. We found that low energy shocks were as successful in patients with a high transthoracic impedance, which was arbitrarily defined as mean + 1 SD—that is >115 Ω, as they were in patients with a transthoracic impedance of $\leqslant 115$ Ω. This accords with a prospective analysis of defibrillation performed in 183 patients where the initial shock was usually 200 J.[12] There was no difference in transthoracic impedance between those who defibrillated and those who did not.[12] This study did not assess energy requirements and included patients who developed ventricular fibrillation late in the resuscitation, generally after an initial brady-asystolic arrest with defibrillation failing in a high percentage of patients.[12] Geuze and de Feijter also suggested that transthoracic impedance was not a useful predictor of defibrillation success when low energy shocks were used.[13] Aylward *et al* investigated electrode-chest wall coupling agents during canine ventricular defibrillation and found that higher transthoracic impedance did not alter the success of countershock.[14]

It has been suggested that transthoracic impedance is an important determinant of defibrillation at energies lower than 200 J. Kerber *et al* found that patients with a transthoracic impedance of >97 Ω had a reduced success rate for defibrillation with $\leqslant 100$ J shocks.[5] However, this effect was not seen with shocks of $\geqslant 200$ J. This study was performed in only 25 patients with ventricular fibrillation and no information was given on the duration of ventricular fibrillation or the amplitude of ventricular fibrillation. In a later study the same group suggested that shocks of 100 J were less effective in patients with a transthoracic impedance of $\geqslant 70$ Ω than in those with a transthoracic impedance of <70 Ω.[6] In this study also, most patients did not have ventricular fibrillation, and of those who did, most developed the arrhythmia in the electrophysiological laboratory.[6] Ventricular defibrillation in these situations may not be representative of true emergency defibrillation. Furthermore, in this study those patients who developed ventricular fibrillation elsewhere—that is in locations other than the electrophysiology or cardiac catheterisation laboratories and required "emergency" defibrillation were excluded from receiving an initial 100 J shock and were treated with an initial shock of 200 J regardless of their transthoracic impedance.[6] Separate transthoracic impedance ranges for patients with different arrhythmias were not given; this is important because the mean (SD) transthoracic impedance for the group was 75 (21) Ω. Our mean transthoracic impedance for ventricular fibrillation patients was significantly higher than this and was similar to that reported by Lerman *et al* who studied patients who developed ventricular fibrillation during electrophysiological testing.[15] Thus the conclusions made by Kerber *et* *al* are based on a mixed group of patients, of whom only some required emergency defibrillation.[6] Extrapolation of these results to the clinical setting has to be viewed with caution. We believe that our patients with ventricular fibrillation are representative of the true emergency clinical situation because in all of them ventricular fibrillation occurred spontaneously and not in the catheterisation laboratory. Unlike other studies[5 6] we specifically excluded patients with atrial flutter and ventricular tachycardia, because these arrhythmias require a fraction of the energy required to convert atrial and ventricular fibrillation.

We found that patients with ventricular fibrillation had higher mean transthoracic impedance (93 (22) Ω) than a group of patients from a previous study undergoing elective cardioversion of atrial fibrillation (69 (16) Ω)($p < 0{\cdot}001$).[7] Because transthoracic impedance is dependent on ionic conduction and therefore related to tissue conductivity, it is not surprising that the dramatic haemodynamic and metabolic effects of cardiac arrest can alter transthoracic impedance. Experimental support for this suggestion is provided by Wojtczak who reported that myocardial tissue resistivity increased with hypoxia.[16] In addition, Childers *et al* found that the tissue resistance of ventricular myocardium increased with ischaemia and they suggested this may be the result of cell swelling, intercellular uncoupling at gap junctions, and membrane disruption.[17] Also, during a cardiac arrest skin blood flow is reduced and there is an increased resistivity of stationary blood.[18]

Because it is the current that actually defibrillates, it would be more satisfactory to use a method for defibrillation that was independent of transthoracic impedance and delivered a constant current to each patient. We have reported our initial experience with a microprocessor controlled current based defibrillator that titrates energy according to each patient's individual transthoracic impedance.[19] This defibrillator has a success rate comparable to conventional defibrillators but it delivers significantly less energy and current per shock.

Single factor analysis identified only the site of the cardiac arrest and prior treatment with antiarrhythmic agents as being significantly associated with the success of the first 200 J shock. These findings were confirmed by multiple regression analysis. Ventricular fibrillation outside hospital was associated with ventricular fibrillation of a longer duration. Though we found no association between the duration of ventricular fibrillation and shock success, others have reported an inverse relation between the duration of ventricular fibrillation and the success of defibrillation.[20] We did not find that transthoracic impedance was higher in patients who had cardiac arrest out of hospital and we found no relation between transthoracic impedance and the duration of ventricular fibrillation.

The effect of antiarrhythmic drugs on success of the first shock is interesting but difficult to explain because this group included patients taking lignocaine, mexiletine, amiodarone, and bretylium tosylate either singly or in various combinations. Because of the small numbers of patients taking each drug, we did not perform individual analyses. It has been suggested that the effects of drugs on transmembrane sodium and potassium currents explains the alterations in the defibrillation threshold.[21] Lignocaine produced a small fall (7%) in canine transthoracic impedance when it was given with pentobarbital anaesthesia.[22] Bretylium tosylate increased the ventricular fibrillation threshold,[23] reduced defibrillation threshold,[24] and can cause chemical defibrillation.[25]

Univariate analysis showed that survival to discharge was poorer among older patients (>70 years), those with transthoracic impedance >115 Ω, when an initial arrest occurred outside hospital, when ventricular fibrillation lasted more than 3 minutes before attempted defibrillation, when there was fine ventricular fibrillation, when the aetiology of ventricular fibrillation was not myocardial infarction, and when more than two shocks were needed to correct ventricular fibrillation. Multiple regression analysis showed that the factors of greatest significance (in rank order) in predicting discharge from hospital were ventricular fibrillation amplitude $\geqslant 0{\cdot}5$ mV, age $\leqslant 70$ years, and the requirement of $\leqslant$ two shocks to correct ventricular fibrillation. Dunn *et al* reported poorer survival to discharge for those receiving five or more shocks[26] to correct ventricular fibrillation at the time of the initial arrest. Weaver *et al* showed that patients who survived had required fewer shocks than patients who died later in hospital (2·6 shocks *v* 3·6).[27] Defibrillation can impair left ventricular function.[28] There appears to be an association between survival and shock energy, because we found that those who were defibrillated by one or two (200 J) shocks had a significantly better survival rate than those who needed more than two shocks (and thus high energy shocks). Campbell *et al* found that of 11 patients in whom shocks of 200 J were unsuccessful and were given 400 J (stored energy) shocks, only five survived to leave hospital.[29] Higher energy shocks produced a higher incidence of atrioventricular block after defibrillation though survival rates were similar.[27] The actual energy delivered to a patient for a given selected energy setting of the defibrillator depends on their transthoracic impedance. High impedance patients receive more energy and develop a lower peak current than low impedance patients. We found that 6/12 patients with a transthoracic impedance of >115 Ω died during the arrest and only one survived to be discharged.

The association of fine ventricular fibrillation with an almost universally poor outcome has been widely reported.[30 31] Fine ventricular fibrillation represents a degeneration induced by metabolic changes, and as ventricular fibrillation continues its amplitude decreases. We found a significant association between fine ventricular fibrillation and ventricular fibrillation lasting more than three minutes. Also, patients with a transthoracic impedance of

$>95\ \Omega$ were more likely to have fine ventricular fibrillation than those with a transthoracic impedance of $\leqslant 95\ \Omega$. Fine ventricular fibrillation is as easy to defibrillate as coarse ventricular fibrillation—we obtained similar success rates both for first shock and for two 200 J shocks. This is similar to the results of another study.[30] The equality of ease of defibrillation accords with the finding that coarse ventricular fibrillation does not reflect greater synchronisation of activity than fine ventricular fibrillation.[32]

Myocardial ischaemia reduced the ventricular fibrillation threshold[33] but did not seem to increase the defibrillation threshold.[34] Moderate ischaemia makes the threshold for ventricular fibrillation fall below control values and severe ischaemia produces a ventricular fibrillation threshold higher than that obtained with moderate ischaemia; thus severe ischaemia may make the ventricle less vulnerable to fibrillation.[35] Ventricular fibrillation with causes other than myocardial ischaemia or infarction is a more sinister development and is usually secondary to other disease processes the severity of which determines the outcome.

1 Crampton R. Accepted, controversial, and speculative aspects of ventricular defibrillation. *Prog Cardiovasc Dis* 1980;23:287–306.
2 Zipes DP, Fischer J, King RM, Nicoll Ade B, Jolly WW. Termination of ventricular fibrillation in dogs by depolarizing a critical amount of myocardium *Am J Cardiol* 1975;36:37–44.
3 Kugelberg J. The interelectrode electrical resistance at defibrillation. *Scand J Thorac Cardiovasc Surg* 1972;6:274–7.
4 Geddes LA, Tacker WA, Schoenlein W, Minton M, Grubbs S, Wilcox P. The prediction of the impedance of the thorax to defibrillating current. *Med Instrum* 1976;10 159–62.
5 Kerber RE, Kouba C, Martins J, Kelly K, Low R, Hoyt R, *et al.* Advance prediction of transthoracic impedance in human defibrillation and cardioversion: importance of impedance in determining the success of low-energy shocks. *Circulation* 1984;70:303–8.
6 Kerber RE, Martins JB, Kienzle MG, Constantin L, Olshansky B, Hopson R, *et al* Energy, current, and success in defibrillation and cardioversion: clinical studies using an automated impedance-based method of energy adjustment. *Circulation* 1988;77:1038–46.
7 Dalzell GWN, Anderson J, Adgey AAJ. Factors determining success and energy requirements for cardioversion of atrial fibrillation: revised version. *Q J Med* 1991;78:85–95.
8 Dalzell GWN, Magee H, Anderson J, Adgey AAJ. Predicted and actual impedance in cardioversion [Abstract]. *Circulation* 1986;74 (suppl II):II–388.
9 Dahl CF, Ewy GA, Ewy MD, Thomas ED. Transthoracic impedance to direct current discharge effect of repeated countershocks. *Med Instrum* 1976;10:151–4.
10 Geddes LA, Tacker WA, Cabler P, Chapman R, Rivera R, Kidder H. The decrease in transthoracic impedance during successive ventricular defibrillation trials *Med Instrum* 1975;9:179–80.
11 Kerber RE, Grayzel J, Hoyt R, Marcus M, Kennedy J. Transthoracic resistance in human defibrillation. *Circulation* 1981;63:676–82.
12 Kerber RE, Jensen SR, Gascho JA, Grayzel J, Hoyt R, Kennedy J Determinants of defibrillation: prospective analysis of 183 patients *Am J Cardiol* 1983;52:739–45.
13 Geuze RH, de Feijter PJ Evaluation of transthoracic countershock with initial energy levels up to 200 J in a coronary care unit *J Electrocardiol* 1985;18:251–8
14 Aylward PE, Kieso R, Hite P, Charbonnier F, Kerber RE. Defibrillator electrode-chest wall coupling agents. influence on transthoracic impedance and shock success. *J Am Coll Cardiol* 1985;6.682–6.
15 Lerman BB, DiMarco JP, Haines DE. Current-based versus energy-based ventricular defibrillation: a prospective study. *J Am Coll Cardiol* 1988,12:1259–64.
16 Wojtczak J. Contractures and increase in internal longitudinal resistance of cow ventricular muscle induced by hypoxia. *Circ Res* 1979;44 88–95.
17 Childers RW, Cope T, Lyon R, Holland R. Tissue resistance in ventricular ischemia [Abstract]. *Circulation* 1979;59 and 60 (suppl II):II–110.
18 Geddes LA, Baker LE. The specific resistance of biological material—a compendium of data for the biomedical engineer and physiologist. *Med Biol Eng* 1967;5·271–93
19 Dalzell GWN, Cunningham SR, Anderson J, Adgey AAJ Initial experience with a microprocessor controlled current based defibrillator. *Br Heart J* 1989;61.502–5.
20 Yakaitis RW, Ewy GA, Otto CW, Taren DL, Moon TE. Influence of time and therapy on ventricular defibrillation in dogs. *Crit Care Med* 1980,8:157–63.
21 Babbs CF. Alteration of defibrillation threshold by antiarrhythmic drugs: a theoretical framework. *Crit Care Med* 1981;9:362–3
22 Kerber RE, Pandian NG, Jensen SR, Constantin L, Kieso RA, Melton J, *et al.* Effect of lidocaine and bretylium on energy requirements for transthoracic defibrillation· experimental studies. *J Am Coll Cardiol* 1986,7:397–405.
23 Chow MSS, Kluger J, DiPersio DM, Lawrence R, Fieldman A Antifibrillatory effects of lidocaine and bretylium immediately postcardiopulmonary resuscitation. *Am Heart J* 1985;110 938–43.
24 Tacker WA, Niebauer MJ, Babbs CF, Combs WJ, Hahn BM, Barker MA, *et al.* The effect of newer antiarrhythmic drugs on defibrillation threshold. *Crit Care Med* 1980, 8:177–80
25 Sanna G, Arcidiacono R Chemical ventricular defibrillation of the human heart with bretylium tosylate. *Am J Cardiol* 1973;32 982–7.
26 Dunn HM, McComb JM, MacKenzie G, Adgey AAJ. Survival to leave hospital from ventricular fibrillation. *Am Heart J* 1986;112:745–51
27 Weaver WD, Cobb LA, Copass MK, Hallstrom AP. Ventricular defibrillation—a comparative trial using 175-J and 320-J shocks. *N Engl J Med* 1982;307:1101–6.
28 Stoddard MF, Labovitz AJ, Stevens LL, Buckingham TA, Redd RR, Kennedy HL. Effects of electrophysiologic studies resulting in electrical countershock or burst pacing on left ventricular systolic and diastolic function. *Am Heart J* 1988;116:364–70.
29 Campbell NPS, Webb SW, Adgey AAJ, Pantridge JF. Transthoracic ventricular defibrillation in adults. *BMJ* 1977;ii:1379–81.
30 Weaver WD, Cobb LA, Dennis D, Ray R, Hallstrom AP, Copass MK. Amplitude of ventricular fibrillation waveform and outcome after cardiac arrest. *Ann Intern Med* 1985;102:53–5.
31 Stults KR, Brown DD, Kerber RE Ventricular fibrillation amplitude predicts ability to defibrillate [Abstract]. *J Am Coll Cardiol* 1987,9 152A.
32 Jones DL, Klein GJ Ventricular fibrillation· the importance of being coarse? *J Electrocardiol* 1984;17 393–400.
33 Burgess MJ, Abildskov JA, Millar K, Geddes JS, Green LS. Time course of vulnerability to fibrillation after experimental coronary occlusion *Am J Cardiol* 1971;27: 617–21.
34 Kerber RE, Pandian NG, Hoyt R, Jensen SR, Koyanagi S, Grayzel J, *et al.* Effect of ischemia, hypertrophy, hypoxia, acidosis, and alkalosis on canine defibrillation. *Am J Physiol* 1983,244:H825–31.
35 Fisher J, Sonnenblick EH, Kirk ES. Increased ventricular fibrillation threshold with severe myocardial ischemia. *Am Heart J* 1982;103.966–72.

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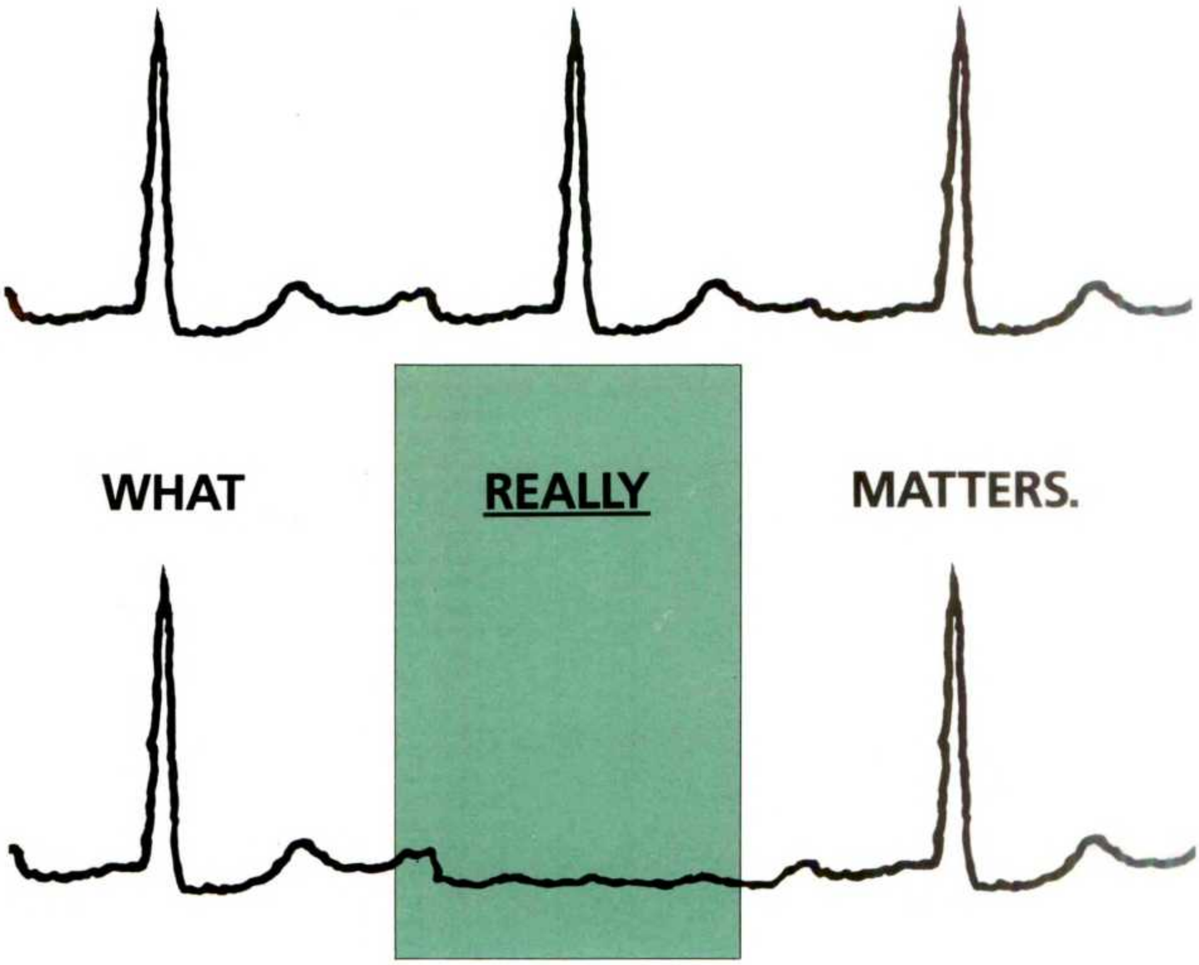

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References
1. Kjekshus, J., and Swedberg, K., *Amer. J. Cardiol.*, 1989, **63**, 26D.
2. Swedberg, K., and Kjekshus, J., *Drugs*, 1990, **39** (Suppl. 4), 49.
3. CONSENSUS Trial Study Group, *New Engl. J. Med.*, 1987, **316**, 1429.

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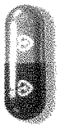

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1. Boult J. Pharm J 1989. 242:180
2. Davis SS & Wilding IR. Nott. Univ. Data on File.
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A quantitative histopathological study of right bundle branch block complicating acute anteroseptal myocardial infarction

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Abstract

The aim of the present study was to evaluate whether necrosis of the right bundle branch is responsible for development of right bundle branch block in acute myocardial infarction. Twenty patients with acute anteroseptal myocardial infarction were studied—10 with right bundle branch block (group A) and 10 without (group B)—to evaluate by serial sectioning the pathological extent of myocardial infarction surrounding the right bundle branch and also that of right bundle branch necrosis. Myocardial infarction reached the right bundle branch more than 8 mm above the moderator band in all of group A, whereas myocardial infarction reached the right bundle branch less than 3 mm above the moderator band in only three patients in group B. Nine hearts in group A showed significant necrosis of the right bundle branch. In group B and in one case with transient right bundle branch block no necrosis was found. The occurrence of right bundle branch block was almost entirely explained by necrosis of the right bundle branch, but transient right bundle branch block did develop without necrosis of the right bundle branch.

Though the outcome in patients with the complication of right bundle branch block in acute anteroseptal myocardial infarction is poor,[1–3] there are few necropsy studies of the atrioventricular conduction system. Some workers concluded that reversible damage or functional impairment of the conducting cells or both have a major role in the development of conduction disturbances,[4 5] whereas others encountered massive necrosis of the bundle branches.[6–8]

We examined the hypothesis that necrosis of the right bundle branch is a determinant of the occurrence of right bundle branch block in acute anteroseptal infarction. We measured the pathological extent of myocardial infarction surrounding the right bundle branch and necrosis of the right bundle branch in hearts from patients in whom right bundle branch block had developed during the course of acute anteroseptal infarction and in patients in whom it had not.

Patients and methods

We studied the morphology of the conduction system in ten hearts from patients who developed right bundle branch block during the course of acute anteroseptal infarction (group A) and compared the changes with those present in ten hearts from patients who died from acute anteroseptal infarction uncomplicated by right bundle branch block. We excluded patients who died within a day of the onset of myocardial infarction to ensure that the pathological analysis of myocardial infarction would be reliable. Acute anteroseptal infarction was diagnosed clinically and confirmed pathologically in both groups. The electrocardiographic criteria for right bundle branch block were a QRS interval that was longer than 0·12 s with a QR configuration in V1 and a slurred S wave in V6.[9 10]

The hearts were examined after fixation in 10% buffered formalin. Stenotic lesions of the epicardial coronary arteries were estimated by taking sections every 3 mm, and stenosis of $\geqslant 75\%$ of the vessel lumen was regarded as significant. Most of the upper (basal) interventricular septum was cut off in blocks approximately 3·5 cm wide and 3·0 cm long according to Lev's method.[11] These blocks contained the atrioventricular conduction system, consisting of the atrioventricular node, the bundle of His, and the left and right bundle branches. These blocks were embedded in paraffin and sectioned (6 μm) serially. We retained every twentieth section and stained it with haematoxylin-eosin, Masson's trichrome stain, and immunohistological stains for myoglobin.

On these sections we histologically determined the extent of the myocardial infarction surrounding the right bundle branch and studied the atrioventricular conduction system. After we had reconstructed the conduction system we subdivided the right bundle branch into three portions.[11 12] The first portion is usually immediately beneath the endocardium, but occasionally deeper in the myocardium, and extends from the bundle branch bifurcation to the septomarginal trabeculum. The second portion consists of an intramyocardial segment in the septomarginal trabeculum. The third portion is subendocardial and runs from the lower border of the septomarginal trabeculum to the base of the anterolateral papillary muscle via the moderator band. We regarded the right

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Clinical details of the study groups

Case	*Age*	*Sex*	*From MI to death*	*From MI to CRBBB*	*Cause of death*
Group A:					
1*	63	M	8 day	3 day	VT/Vf
2	75	M	3 day	<14 h	Cardiogenic shock
3	64	M	4 day	2 h	Cardiogenic shock
4	81	M	6 day	<1 h	Cardiogenic shock
5	71	F	2 day	<14 h	Cardiogenic shock
6	82	M	16 day	<5 day	Cardiogenic shock
7	84	M	2 day	4 h	Cardiogenic shock
8†	75	M	5 day	8 h	VT/Vf
9	64	F	5 day	2 day	Cardiogenic shock
10	57	M	3 day	2 day	CHF
Mean (SD)	71·6 (9·3)		5·4 (4·2)		
Group B:					
11	77	M	8 day		VT/Vf
12	82	F	12 day		VT/Vf
13	68	M	11 day		CHF
14	75	M	2 day		Cardiogenic shock
15	81	M	2 day		CHF
16	65	M	5 day		VT/Vf
17	47	M	2 day		Cardiogenic shock
18	72	F	21 day		Cardiogenic shock
19	55	M	14 day		VT/Vf
20	86	M	3 day		Cardiogenic shock
Mean (SD)	70·8 (12·4)		8·0 (6·1)		

*A case of transient complete atrioventricular block.
†A case of transient CRBBB.
CHF, congestive heart failure; CRBBB, complete right bundle branch block; MI, myocardial infarction; VT/Vf, ventricular tachycardia and/or fibrillation.

bundle branch as necrotic when we found coagulation necrosis of the conducting cells with or without evidence of healing, such as inflammatory cell infiltration and newly formed granulation tissue.[13] We based the estimate of the degree of right bundle branch necrosis on cross sectional area and classified it total (necrosis occupying 100% of the cross section of the right bundle branch), severe (75–90%), moderate (50–74%), and mild (<50%).

Results

CLINICAL FINDINGS

The table shows the clinical summaries including the intervals between onset of myocardial infarction and the onset of right bundle branch block and death. Four patients in group A had right bundle branch block on admission and in six it developed while they were in hospital. In all the patients except one (case 8), right bundle branch block was seen at the time of death. Right bundle branch block had been present for between one and 12 days. Patient 8 had transient right bundle branch block for 28 hours which developed eight hours after the onset of myocardial infarction. Patient 1 also had transient complete atrioventricular block.

EXTENT OF INFARCTION SURROUNDING THE RIGHT BUNDLE BRANCH

All cases showed significant stenoses of the left anterior descending coronary artery, with coronary thrombi in nine of group A and seven of group B. There was a significant lesion proximal to the origin of the first septal branch in nine group A hearts and five group B hearts. Single, double, and triple vessel disease was found in three, five, and two respectively in group A and two, three, and five in group B. Myocardial infarction was seen in the anteroseptal regions. Coagulation necrosis and some healing were identified histologically in all 20 hearts. Infarction adjacent to the right bundle branch was seen in all group A hearts, but in only three group B hearts, in which it was adjacent to the distal right bundle branch.

Figure 1 shows the anatomical relation between the extent of infarction and the right bundle branch. In all the group A hearts, the upper limit of infarction extended around the right bundle branch to more than 8 mm above the moderator band—that is to the proximal half of the second portion of the right bundle branch. In three group B hearts (cases 12, 15, and 16), infarction extended around the right bundle branch to less than 3 mm above the moderator band. In the remaining seven hearts, infarction did not reach the right bundle branch.

NECROSIS OF THE RIGHT BUNDLE BRANCH

Figure 2 shows the extent of right bundle branch necrosis. There was significant necrosis of the right bundle branch in nine of the group A hearts; this was total in three, severe in three, and moderate in three. There was no necrosis of the right bundle branch block in the remaining heart from the patient showing transient right bundle branch block (case 8) and the conducting cells were almost normal except for mild hydropic changes. There was no necrosis in any of the group B hearts, even in the three in which infarction was adjacent to the right bundle branch.

Figure 2 shows that infarction surrounding the right bundle branch did not coincide completely with right bundle branch necrosis. In five group A hearts (cases 3, 4, 5, 7, and 9) the most proximal involvement extended further than the necrosis of the right bundle branch. In the remaining four hearts (one in group A and three in group B) we did not find necrosis of the right bundle branch despite infarction adjacent to the right bundle branch. In three of these (cases 12, 15, and 16), only a small distal portion of the right bundle branch was affected by infarction. In the remaining case (case 8) the

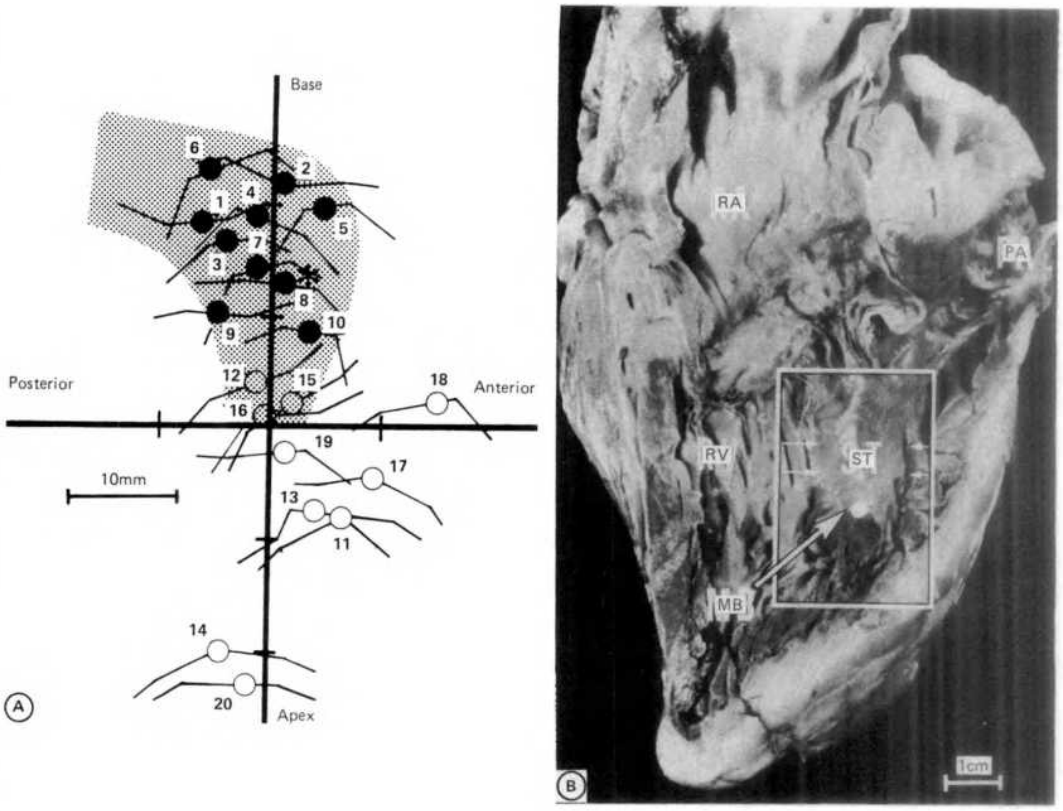

Figure 1 Anatomical relation between margin of myocardial infarction and site of right bundle branch in cases with right bundle branch block and those without.
*(A) Rectangular coordinates on the right ventricular surface of the interventricular septum that correspond to the boxed area in (B). Coordinates intersect at the upper edge of cross section of the moderator band (arrow) where the third portion of the right bundle branch was examined in each heart. The shaded area shows various courses of the right bundle branches in our cases. The margin of infarction closest to the base across the right bundle branch is shown for 13 hearts. In the remaining seven hearts without infarction adjacent to the right bundle branch, the highest point of infarction in the subendocardium of the right ventricular side of the interventricular septum is shown. ●, group A; ○, group B. *A case with transient right bundle branch block (heart 8). RA, right atrium; RV, right ventricle; ST, septomarginal trabeculum.*

right bundle branch was not completely surrounded by infarcted myocardium.

Figure 3 shows that necrosis of the right bundle branch was more severe in the intramyocardial portion than in the subendocardial portion. The intramyocardial segment (that is, the second portion) almost always showed significant necrosis when it was surrounded by infarction, whereas the subendocardial segment (the third portion) rarely showed extensive necrosis. In hearts 3 and 9, however, necrosis of the third portion was unusually extensive. Mural thrombus covered the endocardial surface above the distal right bundle branch in heart 3.

Discussion

Myocardial necrosis adjacent to the bundle branches was found in cases of acute anteroseptal myocardial infarction complicated by conduction disturbances.[4,5] The extent of infarction surrounding the bundle branches, however, was not measured and the difference between the patients with bundle branch block and those without it has not been established. We found that in patients with acute anteroseptal infarction the margin of the necrosis adjacent to the right bundle branch was significantly closer to the base of the septum in those with right bundle branch block (group A) than in those without it (group B). There was

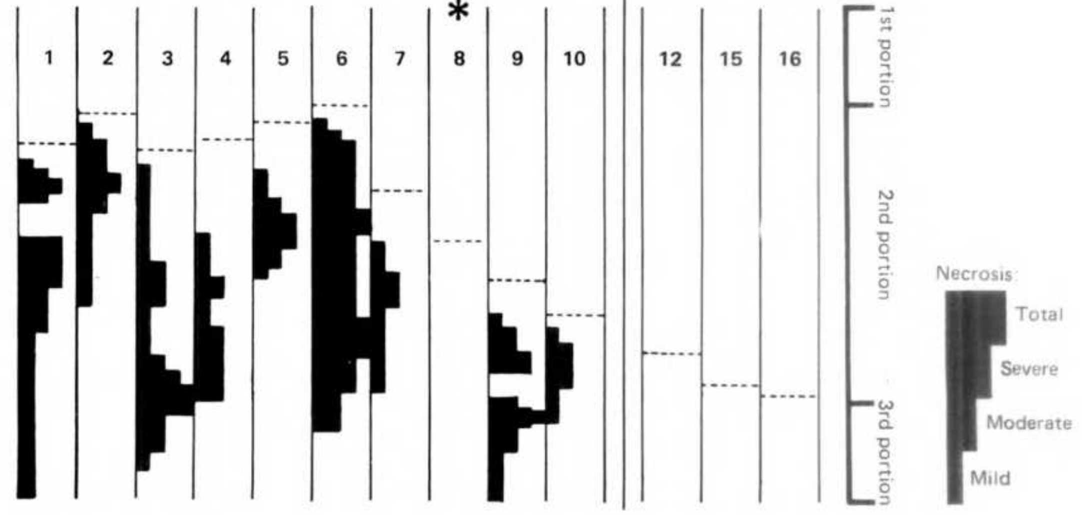

Figure 2 Semiquantitative presentation of necrosis of the right bundle branch in 13 hearts in which infarction reached the right bundle branch. The broken line across the right bundle branch represents the level of the most proximal front line of infarction in each heart. See fig 1 for other symbols.

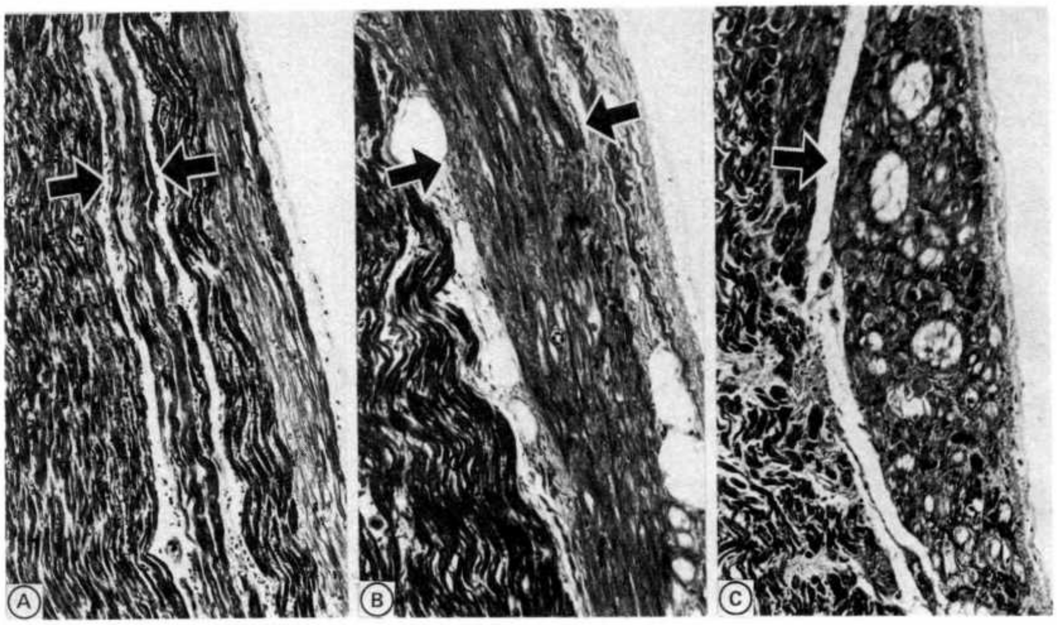

Figure 3 Histopathology of the right bundle branch (Masson's trichrome stain, original magnification × 50). (A) A massive infarction encroaches upon the second portion of the right bundle branch running in the intramyocardium, which shows significant necrosis (arrows). (B) Right bundle branch in the septomarginal trabeculum, 5 mm distal from (A) and unusually running in the subendocardium. It shows no necrosis despite the close proximity of infarction (arrows). (C) Third portion of the right bundle branch in the subendocardium showing no necrosis (arrow). All sections were obtained from heart 5.

no overlap in the extent of the most proximal involvement of the right bundle branch between the two groups.

The present study focused on the complication of right bundle branch block because it can be accurately recognised on electrocardiography and because the morphological features of the right bundle branch simplify quantitative pathological analysis of features such as the degree of right bundle branch necrosis and the anatomical relation between the extent of infarction and the right bundle branch. The right bundle branch is a slender structure 1–2 mm in diameter that runs without branching through the interventricular septum until it reaches the anterolateral papillary muscle of the right ventricle.[11 14]

The second main finding of the present study is the extremely good correlation between the degree of right bundle branch necrosis and the occurrence of right bundle branch block persisting until death. Though the severity of right bundle branch necrosis varied from mild to total, all the cases of persistent right bundle branch block showed significant (moderate or more severe) necrosis. A $\geqslant 50\%$ decrease in number of the conducting cells on cross sections of the conduction system correlated well with chronic bundle branch or atrioventricular blocks.[12 15] We found no necrosis in cases without right bundle branch block (group B).

We found extensive necrosis of the right bundle branch predominantly in the intramyocardial segment (the second portion) and rarely in the subendocardial segment (the third portion) (fig 2). This sparing of the subendocardium might be explained by retrograde perfusion through various left ventricular sinusoidal canals[16] or through the left atrial venous system,[17] or simply by direct diffusion of oxygen from the ventricular cavity through the endocardium.

Opinions vary about the histological lesions of the atrioventricular conduction system in acute anteroseptal infarction with bundle branch block. Some concluded that necrosis does not have a major role in the development of conduction disturbances.[4 5] These complications have been attributed to reversible lesions, such as hydropic cell swelling,[5] whereas others, like us, found that massive bundle branch necrosis was the lesion underlying conduction disturbances.[6–8]

There are several explanations for these different findings about the pathological basis of conduction disturbances. One explanation is uncertainty about the duration of conduction disturbances. In acute myocardial infarction it is impossible to determine whether bundle branch block is transient or persistent, especially when the patient dies within a few days of the onset of infarction. This uncertainty about the duration of the block may influence the histological interpretation. Lie *et al* regarded right bundle branch block lasting more than six days as persistent.[3] At least three cases (cases 1, 4, and 6) in our study fulfilled this criterion. Becker *et al*, however, reported that 18 of 22 patients died within four days of the onset of infarction in their series. This group emphasised reversible ischaemia as an underlying cause of right bundle branch block.[5] Thus the observations of Becker *et al* may represent the pathogenesis of transient block whereas our findings may represent that of persistent block.

Differences in method are another explanation for the discrepancy. We used a serial sectioning technique and showed that there was discordance between the most proximal margin of infarction surrounding the right bundle branch and right bundle branch necrosis; this may arise because the conducting cells are more resistant to ischaemia than the contractile myocardial cells.[18 19] The study of Becker *et al* was based on an examination of several sections of tissue taken from parts containing the assumed course of the conduction system.[5] This method is more likely to underestimate right bundle branch necrosis than serial and quantitative methods.

In the only case with transient right bundle branch block (case 8) that we studied the right bundle branch might have been less injured by ischaemia because the area of infarction surrounding the right bundle branch was not massive, even though it extended along the right bundle branch as far as it did in the cases with persistent right bundle branch block. We agree that degenerative changes or functional disorders of the conducting cells may be responsible for transient conduction disturbances.[4 5] Hackel *et al* suggested non-serious and potentially reversible ischaemia of the conducting cells, the effect of potassium efflux from the infarcted myocardium surrounding the conduction system, or the effects of lytic enzymes released from infiltrating neutrophils as possible mechanisms.[4]

We conclude that right bundle branch necrosis of more than 50% of the cross sectional area is a major determinant for development of persistent right bundle branch block in acute anteroseptal infarction. Though there is a variable gap between the front line of myocardial infarction and that of right bundle branch necrosis, we found that infarction surrounding the right bundle branch more than 8 mm above the moderator band—that is, the proximal half of the second portion—was necessary before significant necrosis of the right bundle branch developed. Transient right bundle branch block, however, can develop when there is no necrosis of the right bundle branch.

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1 Norris RM, Mercer CJ, Croxson MS. Conduction disturbance due to anteroseptal myocardial infarction and their treatment by endocardial pacing. *Am Heart J* 1972,84: 560–6.

2 Scheinman M, Brenman B. Clinical and anatomic implications of intraventricular conduction blocks in acute myocardial infarction *Circulation* 1972;46.753–60.

3 Lie KI, Wellens HJ, Schuilemburg RM, Becker AE, Durrer D. Factors influencing prognosis of bundle branch block complicating acute anteroseptal infarction. The value of His bundle recordings. *Circulation* 1974;50 935–41

4 Hackel DB, Wanger G, Ratliff NB, Cies A, Estes EH Jr. Anatomic study of the cardiac conducting system in acute myocardial infarction. *Am Heart J* 1972,83.77–81.

5 Becker AE, Lie KI, Anderson RH. Bundle-branch block in the setting of acute anteroseptal infarction Clinicopathological correlation. *Br Heart J* 1978,40 773–82.

6 Blondeau M, Rizzon P, Lenegre T Les trouble de la conduction auriculo-ventriculaire dans l'infarctus myocardique recent *Arch Mal Coeur* 1961,54:1104–17

7 Sutton R, Davies MJ. The conduction system in acute myocardial infarction complicated by heart block *Circulation* 1968,38·987–92.

8 Hunt D, Lie JT, Vohra J, Sloman G Histopathology of heart block complicating acute myocardial infarction. Correlation with the His bundle electrogram *Circulation* 1973,48:1252–61.

9 Horan LG, Flowers NC, Tolleson WJ, Thomas JR The significance of diagnostic Q waves in the presence of bundle branch block *Chest* 1970,58 214–21.

10 Chou TC *Electrocardiography in clinical practice* 2nd ed Orlando: Grune and Stratton, 1986.188–9.

11 Lev M, Windran J, Frickson E A method for the histopathologic study of the atrioventricular node, bundle and branches. *Arch Pathol* 1951,52:73–83

12 Fukuda K, Nakata Y, Okada R, Takagi T. Histopathological study on the conduction system of complete right bundle branch block. *Jpn Heart J* 1979,20 831–41.

13 Mallory GK, White PD, Salcedo-Salger J The speed of healing of myocardial infarction. *Am Heart J* 1939,18 647–71.

14 Davies MJ, Anderson RH, Becker AE *The conduction system of the heart* London Butterworth, 1983 41

15 Fukuda K Histopathological study on the conduction system with complete atrioventricular block With special reference to configuration of QRS complex. *Jpn Circ J* 1978;42.1265–78

16 Myers WW, Hong CR. Amount and distribution of Rb86 transport into myocardium from ventricular lumen *Am J Physiol* 1966;211 739–45

17 Moir TW. Study of luminal coronary collateral circulation in the beating canine heart. *Circ Res* 1969;24 735–44.

18 Bagdonas AA, Stucky JH, Piera J, Amer NS, Hoffman BF Effects of ischemia and hypoxia on the specialized conduction system of the canine heart *Am Heart J* 1961;61: 206–18

19 Greenspan K, Cranefield PF. Influence of some factors on oxygen uptake of canine cardiac Purkinje fibers. *Am J Physiol* 1963,204:5–8.

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An antioxidant role for calcium antagonists in the prevention of adrenaline mediated myocardial and endothelial damage

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Abstract

***Objective*—To investigate the mechanism of calcium antagonist mediated cytoprotection against the damaging effects of adrenaline in vivo on cardiac myocytes and human endothelial cells from the umbilical vein.**

***Methods*—Human endothelial cells cultured from the umbilical vein and isolated rat cardiac myocytes were treated with plasma from rats given adrenaline 30 minutes previously with pretreatment with calcium antagonists and without. The effect on indices of cell damage that suggest oxidation stress was determined.**

***Results*—Pretreatment of rats with calcium antagonists before adrenaline administration largely inhibited the cytotoxic effects of their plasma on the two target cells used. Plasma taken from animals not pretreated with calcium antagonists caused release of oxidised glutathione from cells, a fall in intracellular reduced glutathione concentration, a fall in ATP production, and release of angiotensin converting enzyme from the endothelial cells.**

***Conclusion*—Calcium antagonists protect against the cardiotoxic effects of catecholamine by preventing the generation of plasma borne cytotoxic compounds, which are probably free radicals.**

The calcium channel blockers have an established role in clinical practice related to their effect on smooth muscle contractility. Evidence suggests that other functions of this class of drug are likely to be of equal interest. Many of the calcium antagonists inhibit the formation of atherosclerosis, and cause its regression in hyperlipidaemic animal models.[1] Verapamil inhibited cataract formation in alloxan-diabetic rats in a tissue where there are no vascular smooth muscle cells.[2] Methoxy-verapamil inhibited the myocardial injury produced by injection of catecholamines.[3] The mechanism by which calcium channel blockers confer this myocardial protection is not certain. The initial hypothesis was that calcium influx into the myocyte would deplete the intracellular pool of adenosine triphosphate thus provoking an energy collapse and leading to cell death.[4,5] Blockage of the calcium channels should therefore prevent this depletion of adenosine triphosphate. This hypothesis is inconsistent with the fact that adenosine triphosphate depletion does not cause myocardial damage.[6] When isolated rat cardiomyocytes maintained in a medium with a high calcium concentration were treated with isoprenaline or the calcium ionophore A 23187 there was only a transient effect on ATP production.[7,8] It is possible[9,10] that the damage produced in the myocardium by adrenaline or isoprenaline is mediated by free radicals. This hypothesis arose from the observation that catecholamines had no direct effect on cardiac myocytes maintained in vitro[4] whereas plasma taken from rats 30 minutes after injection of adrenaline was profoundly cytotoxic to these cells.[10]

We studied the effect of calcium blockers on the oxidative stress-mediated cytotoxicity of plasma from catecholamine treated animals. The calcium blockers chosen were methoxy-verapamil (D600) and nifedipine, which belong to the phenethylamine and the dihydropiridine groups of calcium antagonists respectively. The effects of each of these in the same model system would show whether these chemically different compounds have a common mode of action in inhibiting catecholamine induced myocardial injury.

Glutathione is the main source of reducing equivalents for protecting the cell against oxidative stress and the main cellular mechanisms for protection against free radical attack are the glutathione peroxidases and glutathione transferase.[11–13] Cells under oxidative stress extrude oxidised glutathione[13,14] and the amount of glutathione extruded is proportional to the degree of oxidative stress. Thus oxidative stress tends to reduce the concentration of intracellular oxidised glutathione[15] and the extent of the decline in the ratio of intracellular reduced glutathione to extracellular oxidised glutathione provides a measure of the degree of oxidative stress imposed on the cells.

To determine the degree of cell damage in each experiment we measured two variables: release into the supernatant of the membrane bound angiotensin converting enzyme from human endothelial cells cultured from the umbilical vein and ATP production, measured in both endothelial cells and in isolated rat cardiomyocytes.

To make these stressed cells more susceptible to damage by free radicals the concentration of glucose in the incubating medium during the experiments was reduced. An increase in oxidised glutathione activates the pentose phosphate pathway. This is one of the main sources of the reduced NADP (NADPH) that is used to regenerate reduced glutathione.

Methods

Endothelial cells derived from umbilical cord veins were established in culture by modifications of the method originally described by Jaffe *et al.*[16] The cells were obtained by digestion with a 0·07% solution of collagenase (type 1 CLS *Clostridium histolyticum,* Worthington) for 20 minutes. The cells were resuspended in medium M199 supplemented with 20% fetal calf serum (Flow), with penicillin (100 μg/ml), streptomycin (100 μg/ml), and amphotericin B (25 μg/ml). We used first passage cells grown on Thermanox coverslips (13 mm) in the experiments.

Cardiomyocytes were prepared from male Sprague-Dawley rats with an average weight of 280 g by a modified Powell and Twist technique.[17] The heart was preperfused with calcium free Krebs's bicarbonate (pH 7·4) containing 0·5 mg/dl of nitroprusside until it was clear of blood, and a 10 mmol/l solution of HEPES and superoxide dismutase (25 units/ml) was added to the perfusion medium.

The cells were treated with plasma obtained from rats injected 30 minutes previously with adrenaline bitartrate (Sigma) at a dose of 5 mg/kg. Rats were also pretreated with 3 mg/kg of methoxyverapamil or 2 mg/kg of nifedipine (Sigma) one minute before being injected with adrenaline. In the experiments with myocytes the cells were incubated for 30 minutes with the plasma. The plasma was then removed and the cells were incubated with Krebs's bicarbonate medium in which glucose was replaced by sucrose. The endothelial cells, after incubation with plasma for 30 minutes, were incubated in Hanks's medium with 5% fetal calf serum in which glucose was again replaced by sucrose.

GLUTATHIONE MEASUREMENT

Reduced glutathione was measured in myocytes according to the method described by Noronha-Dutra *et al.*[10] Total glutathione, released by the cells, was measured in the supernatant after the protein was precipitated with 4% sulphosalicyclic acid containing EDTA (2 mmol/l) and the extracts were neutralised with triethanolamine (diluted 1:5 in water). Glutathione was then estimated by measuring the formation of 5-thio-2-nitrobenzoate at 412 nm with a LKB Ultrospec 4050 spectrophotometer.[18]

The total glutathione in the rat plasma, as measured before the addition of the plasma to the cells, was subtracted from the value for the released glutathione.

ANGIOTENSIN CONVERTING ENZYME ASSAY

Angiotensin converting enzyme was measured in the supernatant from endothelial cells by a fluorimetric assay.[19] Angiotensin converting enzyme was also measured in the rat plasma before it was added to the cells and this value was subtracted from the concentration found in the supernatant.

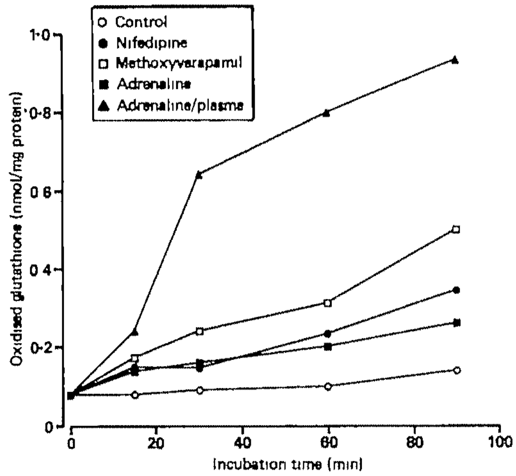

Figure 1 Inhibition of release of oxidised glutathione from isolated rat cardiac myocytes exposed to "adrenaline plasma" from animals pretreated with calcium antagonists.

ATP MEASUREMENT

ATP concentrations were measured both in endothelial cells and myocytes, after freezing and thawing the cells twice, in an LKB-Wallac luminometer by the bioluminescent luciferin-luciferase method.[7]

PROTEIN MEASUREMENT

Protein was measured by the method of Rosebary.[20] All the experiments were repeated at least twice and were performed in duplicate. The figures show the mean of this experiment.

Results

SECRETED GLUTATHIONE

Treatment of isolated cardiomyocytes with plasma taken from animals given catecholamine considerably increased the secretion of glutathione. The increase started about 15 minutes after the plasma was added to the cells' incubating medium (fig 1). The removal of the plasma containing medium from the cells and its replacement by fresh incubating medium had no effect on the extracellular accumulation of secreted glutathione which continued. This

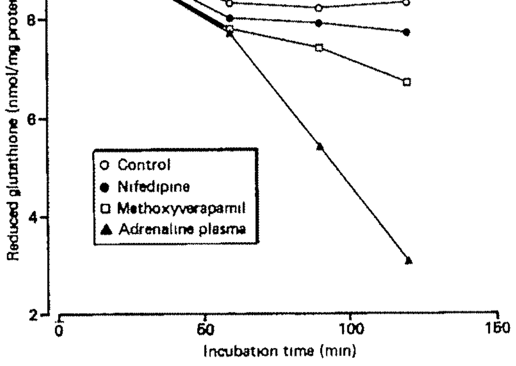

Figure 2 Inhibition of decrease in intracellular reduced glutathione in rat cardiac myocytes exposed to "adrenaline plasma" from animals pretreated with calcium antagonists.

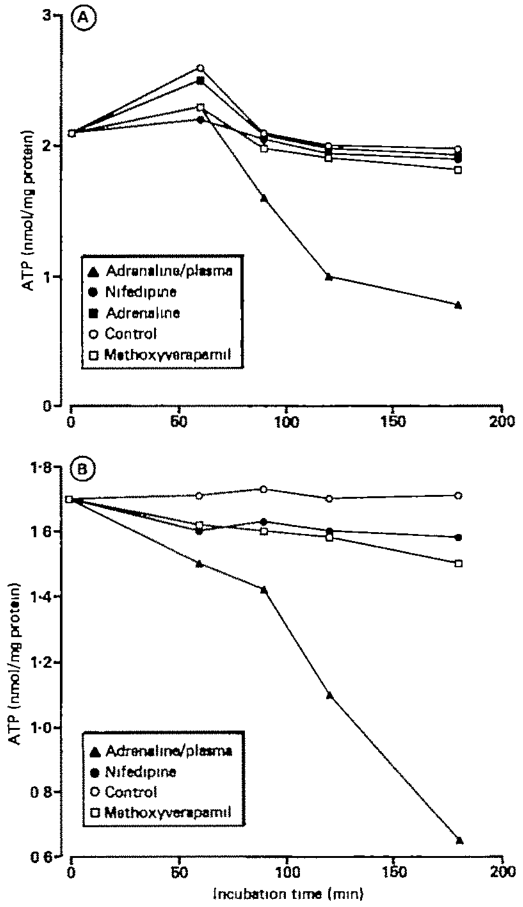

Figure 3 Calcium antagonists inhibit the fall in ATP production by cardiac myocytes (A) and human umbilical vein endothelial cells (B).

suggests that the initial cell injury caused by the plasma from animals treated with adrenaline was irreversible.

The release of glutathione from the cells and by implication the degree of oxidative stress was clearly reduced by treatment with the calcium blockers.

REDUCED GLUTATHIONE

The concentration of reduced glutathione in myocytes was greatly decreased by the treatment with the plasma from animals pretreated with adrenaline (fig 2). In endothelial cells calcium blockers were also effective in preventing the oxidation of glutathione.

ADENOSINE TRIPHOSPHATE MEASUREMENT

The fall in adenosine triphosphate after the treatment of the cells shows that endothelial cells are more susceptible than cardiomyocytes to the toxic effect of the plasma derived from animals pre-dosed with adrenaline (fig 3 A and B). But in both cells the fall in adenosine triphosphate was prevented by the calcium blockers.

ANGIOTENSIN CONVERTING ENZYME

When endothelial cells were treated with plasma taken from animals given adrenaline the concentration of angiotensin converting enzyme, which is localised in the outer part of the plasma membrane of the cells, did not increase in the incubating enzyme if the cells were treated with plasma from animals that had been pre-dosed with calcium blockers before they were given adrenaline (fig 4).

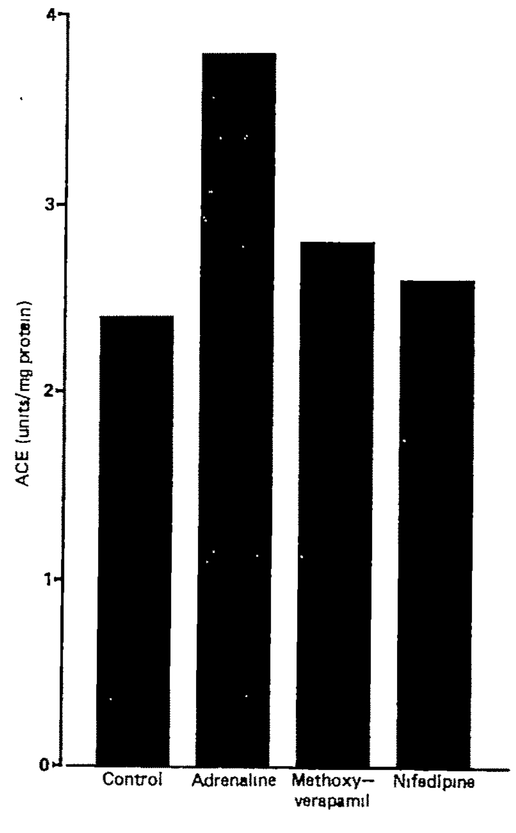

Figure 4 Inhibition of release of angiotensin converting enzyme from endothelial cells exposed to "adrenaline plasma" from animals pretreated with calcium antagonists.

Discussion

Hitherto the best evidence linking calcium antagonists with protection against cardiac injury mediated by free radicals relates to the protection they confer against the damage induced by doxorubicin,[21] where the role of free radicals in the injury is well established. There is evidence from other published reports that calcium antagonists can act as antioxidants.[22-24]

The evidence we present provides further confirmation that adrenaline damage to cardiac myocytes is largely caused by oxidative stress. More importantly it also shows that calcium antagonists largely prevent this stress. Much less glutathione was lost from cells when that plasma came from animals pretreated with calcium blockers. The cytotoxicity of "adrenaline plasma" could not be reproduced when adrenaline was added (in vitro) to the plasma of control (untreated) animals, even at concentrations up to one hundred times higher than would be expected to be found normally in rat plasma.

The protective effect of calcium antagonists in this study was obtained not by treatment of the target cells themselves but by pretreating the animals from which the "adrenaline plasma" was derived. These results suggest therefore that in this model calcium antagonists act by preventing the generation in vivo of the cytotoxic plasma borne compounds that result from the administration of adrenaline.

A role for calcium antagonists in inhibiting the generation of free radicals might serve to protect native low density lipoprotein within the arterial intima from undergoing the oxidative modification that seems to be important in the development of atherosclerotic lesions.[25] This might be an explanation for the inhibition of new lesion formation that has been described in animals and now in humans.[26-28] Equally, calcium antagonists may prevent endothelial damage and thus influence the progression of atherosclerosis.

1 Henry P Calcium antagonists as antiatherogenic agents. *Ann NY Acad Sci* 1988,522:411–9.

2 Fleckenstein A. *Calcium antagonism in heart and smooth muscle Experimental facts and therapeutic prospects*. New York. John Wiley & Sons, 1983:280–5.

3 Steen EM, Woolf N, Powell T, Rowles PM. The effect of a calcium antagonist (D 600) on isoprenaline induced myocardial necrosis in the rat. *Br J Exp Pathol* 1979; 60 335–9.

4 Fleckenstein A. Specific inhibitors and promoters of calcium action in the excitation-contraction coupling of heart muscle and their role in the prevention of production of cardiac lesions In: Harris P, Opie LH, eds. *Calcium and the heart*. London: Academic Press, 1971:135–88.

5 Fleckenstein A, Janke J, Doring HL, Leder O Myocardial fiber necrosis due to intracellular Ca—overload—a new principle in cardiac physiology. In: Dhalla NS, ed. *Recent advances in studies in cardiac structures and metabolism. Myocardial biology vol 4*. Baltimore: University Park Press, 1974:536–41.

6 Jennings RB, Reimer KA, Steenbergen C Jr, Schaper J Total ischaemia III: Effect of inhibition of anaerobic glycolysis. *J Mol Cell Cardiol* 1989;21(suppl I):37–54

7 Noronha-Dutra AA, Steen EM. The effect of isoproterenol and propanolol on ATP levels of isolated cardiac myocytes [Abstract]. *J Pathol* 1982:134:311.

8 Steen EM, Noronha-Dutra AA, Woolf N. The response of isolated heart cells to cardiotoxic concentrations of isoproterenol. *J Pathol* 1982,137:167–76.

9 Noronha-Dutra AA, Steen EM, Woolf N. The correlation between catecholamine and lipid peroxidation induced damage in heart cells. In Piper H, Spieckermann PG, eds. *Adult heart muscle cells* Darmstadt. Steinkopf Verlag, 1984:133–6.

10 Noronha-Dutra AA, Steen EM, Woolf N. Epinephrine-induced cytotoxicity of rat plasma. *Lab Invest* 1988; 59.817–23

11 Singal PK, Beamish RE, Dhala NS. Potential oxidative pathways of catecholamines in the formation of lipid peroxides and genesis of heart disease. *Adv Exp Med Biol* 1983;161 391–5

12 Sies H. Oxidative stress. In: Sies H, eds: *Oxidative stress* London: Academic Press, 1985:1–8

13 Reed DJ. Regulation of oxidative process by glutathione. *Biochem Pharmacol* 1986;35:7–13.

14 Tan KH, Meyer DJ, Belin J, Ketterer B. Inhibition of microsomal lipid peroxidation by glutathione and glutathione transferases B and AA *Biochem J* 1984;220:243–52.

15 Adams AJ, Lautterburg BH, Mitchell JR Plasma glutathione and disulpide in the rat. regulation and response to oxidative stress. *J Pharmacol Exp Ther* 1983;227·749–56.

16 Jaffe EA, Nachman RL, Becker CG, Minick CR Culture of human endothelial cells derived from umbilical veins. Identification of morphologic and immunologic criteria *J Clin Invest* 1973;52:2745–56

17 Powell P, Twist VW. A rapid technique for the isolation and purification of adult cardiac muscle cells having respiratory control and a tolerance to calcium. *Biochem Biophys Res Commun* 1976,72:327–34.

18 Akerboom PM, Sies H. Assay of glutathione, glutathione disulfide, and glutathione mixed disulfides in biological samples. *Methods Enzymol* 1981;77 373–6

19 Friedland J, Silverstein E A sensitive assay for serum angiotensin-converting enzyme. *Am J Clin Pathol* 1976; 66.416–24.

20 Rosebery AL. Protein measurement with folin/phenol reagent. *J Biol Chem* 1953;193:265–72.

21 Milei J, Vazquez A, Boveris A, *et al*. The role of prenylamine in the prevention of adriamycin-induced cardiotoxicity. A review of experimental and clinical findings. *J Int Med Res* 1988,16.19–30

22 Kobayashi A, Yamashita T, Kaneko M, Hayashi H, Yamazaki N. Effect of verapamil on experimental cardiopathy in the Syrian hamster *J Am Coll Cardiol* 1987;10 1128–38.

23 Kaneko M, Lee SL, Wolf CM, Dhalla NS. Reduction of calcium channel antagonist binding sites by oxygen free radicals in rat heart *J Mol Cell Cardiol* 1989,21:935–43

24 Ondrias K, Misik V, Gergel D, Stasko A. Lipid peroxidation of phosphatidylcholine liposomes depressed by the calcium channel blockers nifedipine and verapamil and by the antiarrhythmic-antihypoxic drug stobadine. *Biochim Biophys Acta* 1989;1003:238–45.

25 Steinberg D, Parthasarathy S, Carew T, Khoo J, Witzum J Beyond cholesterol. Modifications of low-density lipoprotein that increases its atherogenicity. *N Engl J Med* 1989;320 915–24

26 Loaldi A, Polese A, Montorsi P, *et al*. Comparison of nifedipine, propanolol and isosorbide dinitrate on angiographic progression and regression of coronary arterial narrowings in angina pectoris. *Am J Cardiol* 1989;64.433–9.

27 Lichtlen PR, Hugenholtz PG, Rafflenheul W, Herker H, Jost S, Deckers JP. Retardation of the angiographic progression of coronary artery disease in man by the calcium channel blocker nifedipine. Results of the International Nifedipine Trial on Antiotherosclerotic Therapy (INTACT). *Lancet* 1990,i 1109–13

28 Waters D, Lesperance J, Theroux P, *et al*. A controlled clinical trial to assess the effect of a calcium channel blocker on the progression of coronary atherosclerosis. *Circulation* 1990;82·1940–53.

Br Heart J 1991;65:326–31

Histopathological validation of high frequency epicardial echocardiography of the coronary arteries in vitro

A Kenny, C A Fuller, N R B Cary, L M Shapiro

Abstract

The accuracy and reliability of measurement of coronary artery dimensions and detection of atherosclerotic lesions by high frequency epicardial echocardiography were compared with histopathological results. Ten pressure perfused human hearts were examined in vitro with a 10 MHz (Diasonics) transducer and a 7·5 MHz (Vingmed/Sonotron) transducer. There was close agreement between ultrasound and pathological measurements of coronary artery luminal diameter. Qualitative changes in wall structure such as diffuse wall thickening and calcification were readily identified; however, the resolution of the transducers was not high enough accurately to measure wall dimensions in normal coronary arteries. Coefficient of variation measurements for intra and inter observer variability (5·2% and 6·9% respectively) showed excellent reproducibility. The technique was accurate in identifying atherosclerotic lesions, imaging arteries distal to an occlusion, locating deeply sited arteries, and identifying complete obliteration of an artery.

Intraoperative video playback and transducer miniaturisation may minimise problems caused by cardiac movement and restricted access. With these developments intraoperative assessment of coronary artery disease may become a real possibility.

High frequency epicardial echocardiography directly images the coronary artery lumen and wall. Intraoperative assessment of coronary artery anatomy by this technique may help to identify optimal sites for anastomoses by showing the coronary artery tree distal to the occluded segments. In addition, it may prove possible to identify stenotic lesions and perhaps even disease not detected at coronary angiography. To assess the accuracy and reliability of high frequency epicardial echocardiography we studied pressure perfused human hearts and compared the results with the histopathological examination.

Patients and methods

Human hearts were obtained at necropsy (eight hearts) or at orthotopic transplantation (two hearts). The coronary arterial tree was fixed with formalin at physiological pressure by the method described by Thomas and Davies.[1] This method fixes the epicardial coronary arteries in a distended state so that they have the same shape and size as in life.

ULTRASOUND EQUIPMENT

Five hearts were studied with a Diasonics CV 250 unit and 10 MHz small parts/vascular transducer. The 10 MHz transducer measures 15 cm long, 5 cm wide, and 2·5 cm deep approximately. It has a depth of field of 3–4 cm and the imaging crystal is 13 mm in diameter with a built-in fluid offset. The phantom point lateral and axial resolution of the transducer are 0·8 mm and 0·3 mm respectively. We then studied another five hearts with a Vingmed/Sonotron CFM 750 unit and 7·5 MHz duplex transducer when it became available. This transducer has a contact surface of 4 cm × 1·5 cm approximately and is 11 cm long. It has a built-in standoff and the axial resolution of this transducer operating at a frequency of 6·2 MHz is <0·5 mm.

ULTRASOUND TECHNIQUE

The hearts were immersed in a water tank and any air bubbles present eliminated by compression of the arteries under water. Imaging was then performed by one operator who was unaware of the presence of coronary atherosclerosis. The handheld transducer was placed over the epicardial surface of the heart and moved along the course of the artery being imaged to obtain longitudinal and cross sectional images. Simultaneous videotape recording was performed for analysis later. Ultrasound measurements were made on freeze frame images by internal electronic calipers. Measurements were confined to high quality images. The location along the coronary artery from which the echocardiographic image and measurements were obtained was marked with a metal staple in the adjacent epicardium. For the pathological measurements we used calipers to measure directly the arterial lumen of the marked arterial segments. Ultrasound measurements of wall thickness were compared with measurements on histological sections from paraffin processed transverse cut blocks. The intra and inter observer variabilities of high frequency epicardial echocardiography were measured to assess the reproducibility of the technique. Thirty randomly chosen images, 15 from each transducer, were reanalysed by the same

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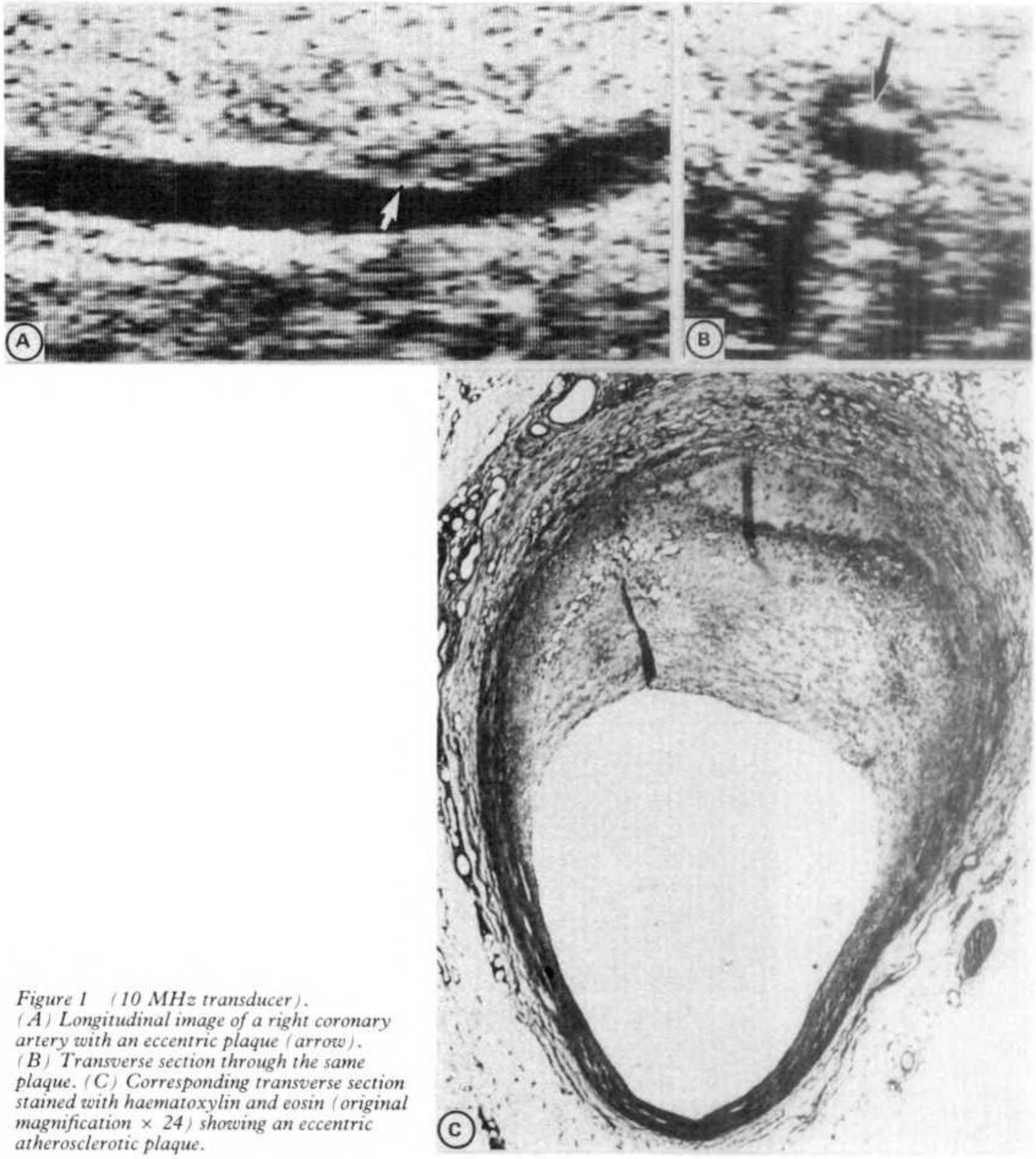

Figure 1 (10 MHz transducer). (A) Longitudinal image of a right coronary artery with an eccentric plaque (arrow). (B) Transverse section through the same plaque. (C) Corresponding transverse section stained with haematoxylin and eosin (original magnification × 24) showing an eccentric atherosclerotic plaque.

observer two weeks later. Another observer analysed the same 30 images independently.

STATISTICAL ANALYSIS

Agreement between ultrasound and pathological measurements of vessels was expressed as the mean plus or minus two standard deviations of the differences between the two methods. Intra and inter observer variability were assessed by the coefficient of variation.

Results

VISUALISATION OF CORONARY ARTERIES

Thirty six coronary arteries were studied in 10 hearts (14 with the 10 MHz and 22 with the 7·5 MHz transducer). The luminal diameter ranged from 0·7 mm to 5·0 mm.

The right coronary artery was successfully imaged in eight hearts (figs 1 and 2). The right coronary artery was not imaged in two hearts: in one because perfusion fixation had resulted in collapse of the artery and in the other because of occlusion along the length of the artery which was confirmed at dissection.

The left anterior descending artery was visualised from the bifurcation of the left main coronary artery to the cardiac apex in eight hearts. The major diagonal branches and septal branches of the left anterior descending artery were also imaged (figs 3, 4, and 5). The left anterior descending coronary artery was noted to be occluded in the mid-segment in two hearts and this was confirmed at dissection. It was possible to image by ultrasound the artery distal to the occluded segment in both these hearts (figs 3E and 5E). In one of these cases the artery distal to the occlusion was a bridged intramyocardial vessel and this was easily located with ultrasound (fig 3E).

The circumflex artery was imaged with the 7·5 MHz transducer in four hearts. This artery was not imaged in one heart because of occlusion along its length; this was confirmed at dissection. The circumflex artery was imaged in two of the five hearts by the 10 MHz transducer. A first obtuse marginal branch of the circumflex coronary artery was also imaged. We did not image the circumflex coronary artery in two transplant recipient hearts because it had been transected. The circumflex coronary artery was occluded along its length in the fifth heart.

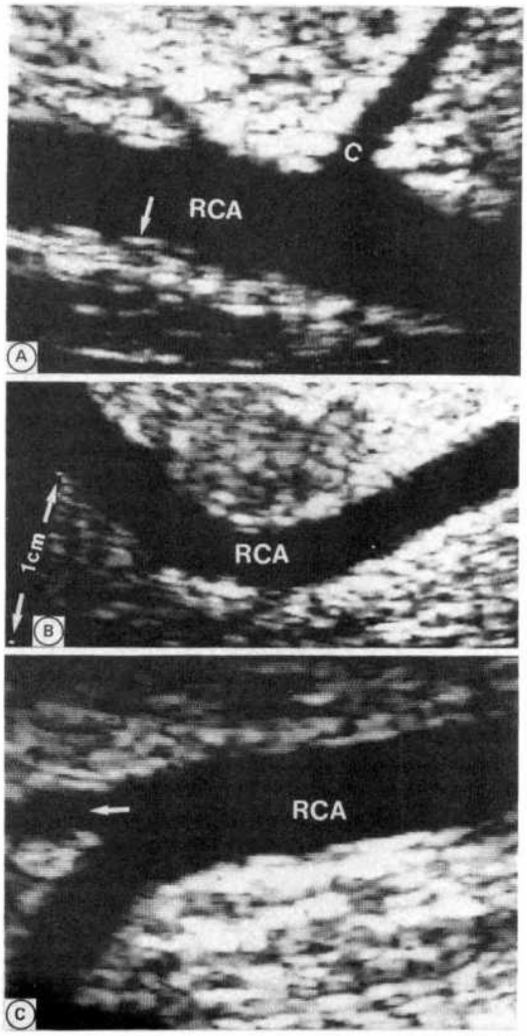

Figure 2 (7·5 MHz transducer). (A) Normal right coronary artery with conus branch (C) and a line which may represent arterial wall (arrow). (B) Normal right coronary artery in atrioventricular sulcus. (C) Normal right coronary artery with right ventricular branch (arrow). RCA, right coronary artery.

MEASUREMENT RELIABILITY AND REPRODUCIBILITY

The coefficients of variation for intra and inter observer measurements (5·2% and 6·9% respectively) showed the reproducibility of the technique was acceptable.

COMPARISON OF ULTRASOUND AND HISTOPATHOLOGICAL MEASUREMENTS

We performed 59 measurements of coronary artery luminal diameter (0·7–5·0 mm) (33 with the 10 MHz transducer and 26 with the 7·5 MHz transducer). There was close agreement between measurements of coronary artery luminal diameter determined by high frequency epicardial echocardiography and measurements made when the corresponding segments of arteries were dissected. The standard deviation of differences between pathological and ultrasonic measurements of luminal diameter was 0·12 mm with a mean difference of −0·01 mm. There was therefore a less than 5% chance of either underestimating the pathological dimension by 0·25 mm or of overestimating it by 0·22 mm by the use of echocardiography. High frequency epicardial echocardiography readily identified qualitative changes in wall structure such as diffuse wall thickening and calcification (fig 3D). In normal coronary arteries, however, it was not possible to measure the arterial wall because it was below the resolution of both transducers. We did note a line adjacent to the lumen which though it was too thick to be the endothelium may be the normal arterial wall (figs 2A and 4D).

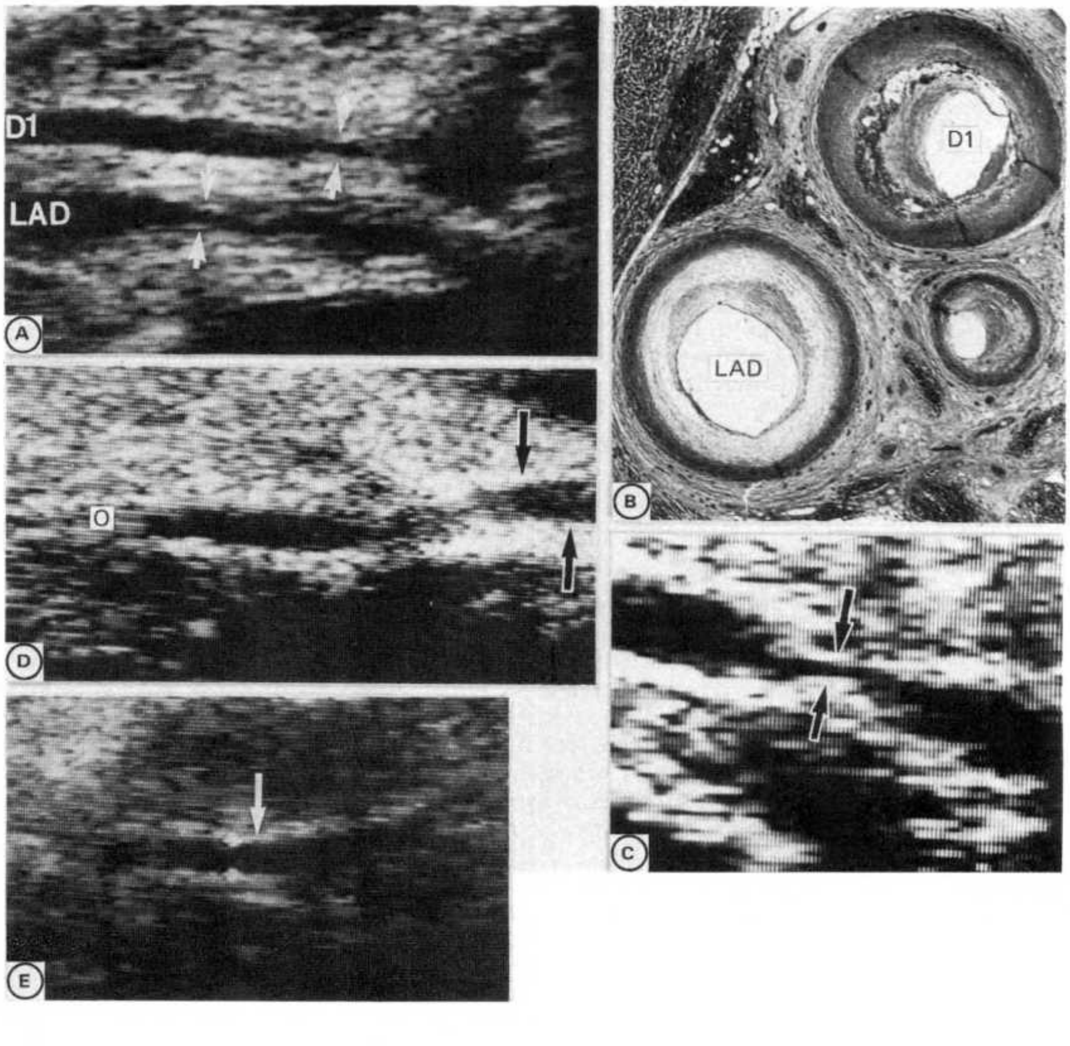

Figure 3 (10 MHz transducer). (A) Severe stenoses (arrows) in left anterior descending artery (LAD) and first diagonal branch (D1) with corresponding transverse section (B) stained with haematoxylin and eosin (original magnification × 17) showing both arteries with concentric intimal thickening, which was more pronounced in the first diagonal. (C) Severe stenosis of the proximal left anterior descending artery (arrows). (D) A severely diseased left anterior descending artery with thickened wall (black arrow) and irregular lumen that eventually becomes occluded (○). (E) A site 2 cm distal to the obstruction shows a deeply sited, thin walled normal myocardial bridged segment of the same artery (white arrow).

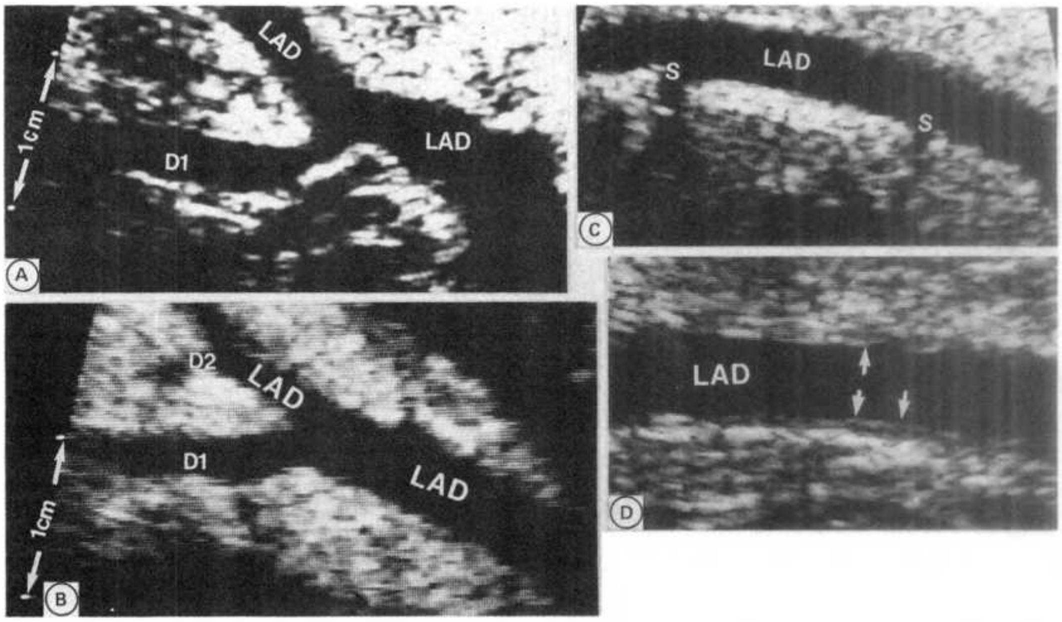

Figure 4 (7·5 MHz transducer). (A) Normal left anterior descending artery (LAD) and first diagonal branch (D1). (B) Normal left anterior descending artery with first and second (D2) diagonal branches. (C) Normal left anterior descending artery with two septal branches (S). (D) Normal left anterior descending artery with clearly defined line which may represent arterial wall (arrows).

DETECTION OF CORONARY ATHEROSCLEROSIS

All lesions detected by ultrasound were examined by histological section. Ultrasonographically normal segments of coronary arteries were also sectioned. There was complete agreement between the two methods with respect to the presence or absence of lesions.

Discussion

Coronary angiography, which is the standard method of evaluating coronary artery disease, has some limitations. Pathological and physiological studies suggest that coronary angiography underestimates the extent and severity of coronary artery disease.[2–4] Complete occlusion of an artery at angiography limits information on the distal coronary arterial bed and its suitability for insertion of bypass grafts. Visually estimated percentage diameter narrowing on coronary angiography as a measure of the severity of stenosis is not universally accepted, especially in lesions of intermediate severity.[5,6] These limitations of coronary angiography suggest that the preoperative information provided to the surgeon by angiography may not always be optimal. Imaging of coronary arteries with a commercial high frequency epicardial transducer may therefore provide useful information supplementary to the coronary angiogram.

High frequency epicardial echocardiography with a high resolution transducer to image the coronary arteries was first described by Sahn *et al* in 1982.[7] Epicardial placement of the transducer allows longitudinal and cross sectional imaging of the coronary arterial lumen and wall; whereas angiography provides a longitudinal image of contrast in the arterial lumen and only provides an image of the arterial wall if calcification is present. Previous studies have validated the accuracy of high frequency epicardial echocardiography in assessing the luminal diameter of the coronary artery and the wall dimensions in living animal models.[8–10] The technique has not been validated with either a 10 MHz or 7·5 MHz transducer. McPherson *et al* are the only other group to have validated high frequency epicardial echocardiography by studying human hearts in vitro.[11] They established the accuracy of a 12 MHz transducer in assessing coronary artery luminal and wall measurements in vivo and also in vitro using five human postmortem hearts. However, the ultrasound measurements were performed on the pressure perfused hearts before formalin fixation and compared with histological measurements on formalin and paraffin processed sections. The histological measurements are therefore subject to fixation artefacts. Arterial shrinkage occurs and this technique has been shown to alter measurements by up to 10%.[12] We performed ultrasound measurements on the formalin fixed, pressure perfused heart and subsequently made pathological measurements at dissection. In this way we avoided potential errors in comparing ultrasound measurements of luminal diameter with measurements on histological sections with possible fixation and shrinkage artefacts.

We found the technique to be accurate and reliable for measuring coronary artery luminal diameter. Though the resolution of the transducers was not sufficient accurately to identify the interface between the arterial wall and adjacent epicardium in thin normal arterial walls, qualitative changes in wall structure and calcified and fibrotic plaques were readily identified (figs 1, 3A, 5A, and 5B). Visualisation of a coronary artery distal to an occlusion, which may be difficult to assess with angiography, was also possible with high frequency epicardial echocardiography (figs 3E, and 5F). This is likely to be useful in identifying a suitable site for graft insertion. When an artery was not located by ultrasound pathological examination confirmed that the artery was occluded along its entire length. This may be useful during operation because it may prevent the unnecessary delay of searching for an obliterated artery. Accurate measurement of luminal diameter and delineation of atherosclerosis may also identify arteries that are diffusely

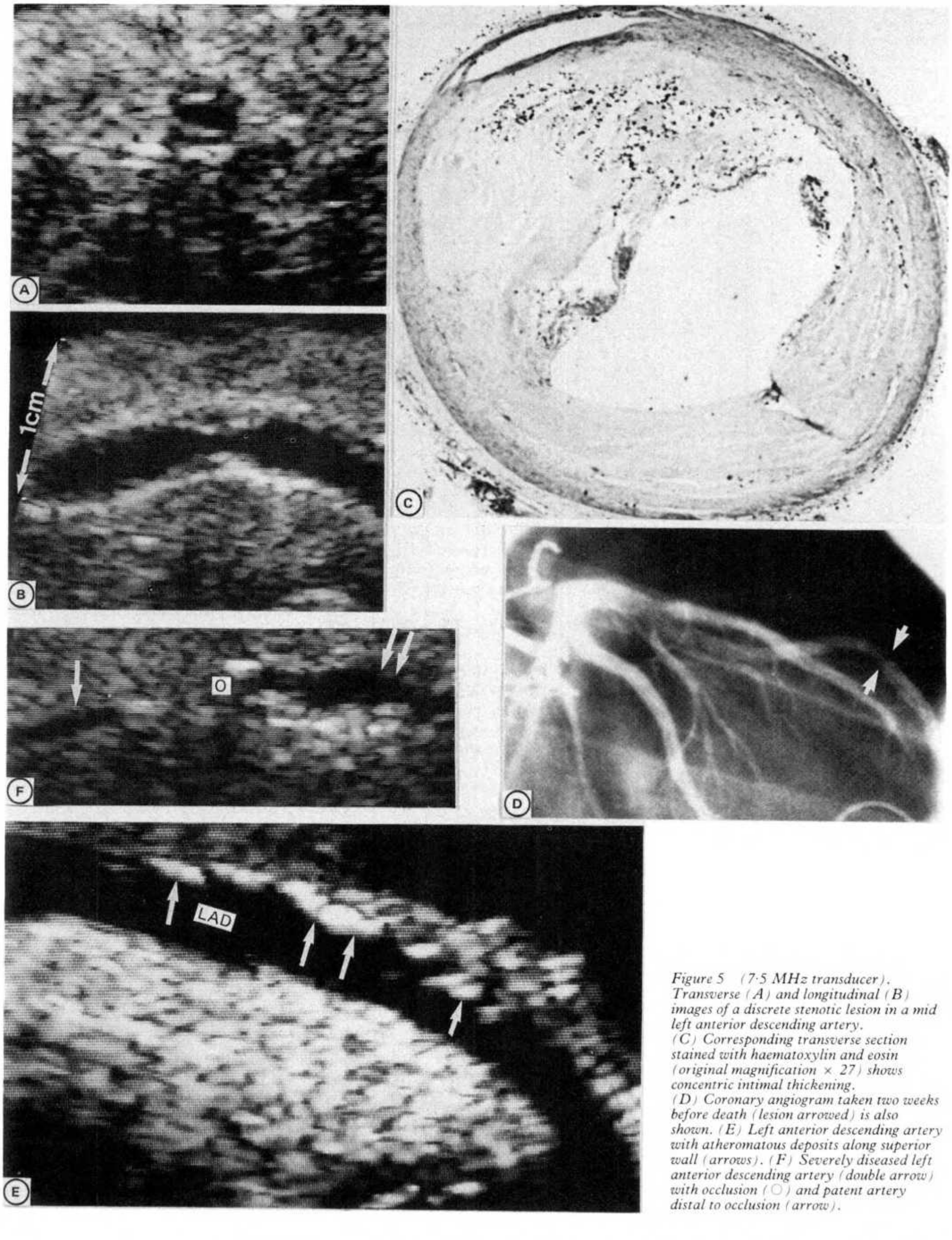

Figure 5 (7·5 MHz transducer). Transverse (A) and longitudinal (B) images of a discrete stenotic lesion in a mid left anterior descending artery. (C) Corresponding transverse section stained with haematoxylin and eosin (original magnification × 27) shows concentric intimal thickening. (D) Coronary angiogram taken two weeks before death (lesion arrowed) is also shown. (E) Left anterior descending artery with atheromatous deposits along superior wall (arrows). (F) Severely diseased left anterior descending artery (double arrow) with occlusion (O) and patent artery distal to occlusion (arrow).

diseased and too small to accept a graft. We also showed that deeply sited arteries can be readily identified (fig 3E). Both transducers produced satisfactory images, and though one would expect the 10 MHz transducer to have better resolution than the 7·5 MHz transducer, we found that the 7·5 MHz transducer produced qualitatively better images. The 7·5 MHz transducer is a more recently developed transducer and its image quality has been improved by recent technical advances. The smaller 7·5 MHz transducer will also allow Doppler examination of the coronary blood flow, but its size will limit examination of the coronary artery tree in vivo to the left anterior descending and proximal right coronary arteries.

High frequency epicardial echocardiography with a 7·5 MHz or 10 MHz transducer accurately and reproducibly measured coronary artery luminal diameter, detected qualitative changes in wall structure, and delineated stenotic lesions. In addition, it located deeply sited vessels, visualised an artery distal to an occlusion, and showed whether an artery is completely obliterated.

We have performed several preliminary studies in patients undergoing cardiac surgery. Cardiac movement and restricted access have proved to be the main obstacles to intraoperative imaging of coronary arteries. Videotape recording and rapid playback facilities have enabled detailed analysis of arteries intermittently visualised during the cardiac cycle. We are about to assess a new 7·5 MHz finger profile transducer that should greatly improve access to the right coronary and circumflex arteries.

1 Thomas AC, Davies MJ. The demonstration of cardiac pathology using perfusion-fixation. *Histopathology* 1985; 9 5–19
2 Arnett EN, Isner JM, Redwood DR, *et al* Coronary artery narrowing in coronary heart disease. comparison of cineangiographic and necropsy findings *Ann Intern Med* 1979, 91.350–6
3 Vlodaver Z, Frech R, Van Tassel RA, Edwards JE Correlation of the antemortem arteriogram and the postmortem specimen *Circulation* 1973,47:162–9
4 White CW, Wright CB, Doty DB, *et al* Does visual interpretation of the coronary arteriogram predict the physiologic importance of a coronary stenosis? *N Engl J Med* 1984;310·819–24
5 Marcus ML, Skorton DJ, Johnson MR, Collins SM, Harrison DJ, Kerber RE Visual estimates of percent diameter coronary stenosis. "a battered gold standard" *J Am Coll Cardiol* 1988;11.882–5
6 Gould KL. Percent coronary stenosis· battered gold standard, pernicious relic or clinical practicality? *J Am Coll Cardiol* 1988,11 886–8
7 Sahn DJ, Barret-Boyes BG, Graham K, *et al* Ultrasonic imaging of the coronary arteries in open-chest humans evaluation of coronary atherosclerotic lesions during cardiac surgery *Circulation* 1982,**66** 1034–44
8 McPherson D, Armstrong M, Marcus M, Kieso R, Megan M, Kerber R Evaluation of the coronary arterial wall and lumen by high frequency 2-dimensional epicardial echocardiography comparison with histologic measurements [Abstract] *J Am Coll Cardiol* 1984,3.565
9 McPherson DD, Kieso RE, Marcus ML, Kerber RE In vivo validation of high frequency epicardial echocardiography for coronary arterial measurements *Circulation* 1984,70(suppl 11) 11–393.
10 McPherson DD, Armstrong M, Rose E, *et al.* High frequency epicardial echocardiography assessment of coronary arteries· further validation [Abstract] *J Am Coll Cardiol* 1985,5.387
11 McPherson DD, Armstrong M, Rose E, *et al* High frequency epicardial echocardiography for coronary artery evaluation· in vitro and in vivo validation of arterial lumen and wall thickness measurements *J Am Coll Cardiol* 1986,8·600–6
12 Bond MG, Insull W Jr, Glagov S, Chandler AB, Cornhill JF, eds *Clinical diagnosis of atherosclerosis-quantitative methods of evaluation* New York Springer-Verlag, 1983 11–35, 265–82, 283–303.

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Myocardial infarction in childhood: clinical analysis of 17 cases and medium term follow up of survivors

David S Celermajer, Gary F Sholler, Robert Howman-Giles, John M Celermajer

Abstract

Between 1979 and 1989 17 patients aged two months to 12 years with acute myocardial infarction of any cause (other than after cardiac surgery) were seen at a children's hospital. Eight died from three days to three years after diagnosis (overall mortality 47%). The nine survivors, now aged 2–17 years, have been followed for one to 10 years (mean follow up five years) after infarction. The commonest causes of myocardial infarction in this series were anomalous origin of left coronary artery from the pulmonary artery (six patients (35%)) and Kawasaki disease (five patients (27%)). The main symptoms of acute myocardial infarction were dyspnoea, vomiting, and difficulty feeding. Diagnosis was made in all patients by electrocardiography and confirmed by echocardiography, cardiac catheterisation, or at operation. All survivors were symptom free with excellent exercise capacity. The left ventricular ejection fraction in survivors ranged from 21% to 66%, and only one child was on regular cardiac medications. There were no cases of late sudden death. Twenty four hour Holter monitoring performed on survivors was normal (seven) or showed minor abnormalities only (one), suggesting that serious arrhythmia is rare after paediatric myocardial infarction.

Myocardial infarction in children had a high early mortality; however, the incidence of serious arrhythmia was low in the survivors, who had a good exercise tolerance even when the left ventricular ejection fraction was low.

Myocardial infarction is rare in infancy and childhood.[1,2] There have been several reports of myocardial infarction complicating Kawasaki disease,[3-6] anomalous coronary arteries,[7] coronary embolus,[8] myocarditis,[9,10] chest trauma,[11,12] and various rare paediatric diseases.[13-15] But there has been no reported systematic follow up of a considerable number of children with non-operative myocardial infarction from all causes.

We therefore collected clinical data and systematically investigated patients with proven myocardial infarction from our hospital to examine the clinical profile of those affected and evaluate the state of survivors.

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Patients and methods

We reviewed the records of all children with typical electrocardiographic findings of acute myocardial infarction seen at the Royal Alexandra Children's Hospital, Sydney, between February 1979 and February 1989.

Records of all necropsies carried out at the hospital over that time and echocardiography or operative reports of high risk conditions (that is Kawasaki disease and anomalous left coronary artery) were also examined to detect any additional cases, but none was found.

Survivors underwent a series of non-invasive investigations between July and September 1989. Twelve lead electrocardiography, cross sectional, and Doppler echocardiography with particular attention to left ventricular wall motion and left ventricular fractional shortening, and 24 hour Holter monitoring (Hewlett Packard 43400B patient analyser) were carried out by standard techniques.[16,17] Bicycle or treadmill exercise testing was performed by incremental increases in workload in the standard manner, as described elsewhere.[18-20] Predicted values for pulse and blood pressure response, and for maximum workload for age, size, and sex were obtained from standard references.[21,22]

Stress thallium-201 myocardial scans were performed after an intravenous infusion of dipyridamole (0·56 mg/kg) over four minutes.[23,24] Thallium-201 citrate adjusted for body weight (1·75 mBq/kg) with a minimum dose of 15 mBq was administered at eight minutes. Planar imaging in the anterior, left anterior oblique 40°; left anterior oblique 60°; and left lateral positions was performed with a Starcom 400 AT gamma camera. Images were taken at five minutes and at three hours after the injection of thallium-201. Computer enhancement of images and circumferential count profiles were performed. Images were divided into five equal ventricular segments as previously described.[25]

Radionuclide gated heart pool scans were performed at rest by electrocardiographically synchronised blood pool imaging of red blood cells labelled in vivo with technetium-99m.[26] Images were acquired in the anterior, modified left anterior oblique, and left lateral positions. We used a small field of view 300 A General Electric gamma camera fitted with high resolution 30° slant hole collimator that was interfaced with a DEC gamma 11 (PDP-11/34) computer system. Images were obtained as 24 frames in a 64 × 64 matrix and were analysed for evidence of regional wall motion abnor-

Table 1 Data on 17 patients with paediatric myocardial infarction

Case	*Sex*	*Age at MI*	*Diagnosis*	*Period of follow-up*	*Operation/age*	*Outcome*
1	M	3 mnth	ALCA	10½ yr	ALCA repair/5 yr	Alive
2	F	4 mnth	ALCA	2¼ yr	ALCA repair/5 mnth	Alive
3	F	3 mnth	ALCA	7½ yr	ALCA repair/9 mnth	Alive
4	M	10 mnth	KD	2 yr	—	Alive
5	F	14 mnth	KD	4½ yr	—	Alive
6	M	18 mnth	KD	3 yr	—	Alive
7	M	6 mnth	KD	4 yr	—	Alive
8	M	9 yr	Trauma	8 yr	LVAn/12 yr	Alive
9	F	12 yr	Myo	1 yr	—	Alive
10	F	10 mnth	Myo	16 mnth	—	Dead
11	F	4 mnth	ALCA	4 mnth	ALCA repair/8 mnth	Dead
12	M	3 mnth	Embolus	6 mnth	—	Dead
13	F	6 mnth	ALCA	1 mnth	—	Dead
14	F	2 mnth	Fibrosis	2 mnth	—	Dead
15	F	4 mnth	ALCA	3 yr	ALCA repair/5 mnth	Dead
16	F	2 yr	KD	3 days	—	Dead
17	F	8 yr	H/T	3 days	—	Dead

ALCA, anomalous origin of left coronary artery, Embolus, coronary embolus; Fibrosis, internal fibrosis of coronary artery; H/T, hypertension with renal failure, KD, Kawasaki disease, LVAn, left ventricular aneurysmectomy; MI, myocardial infarction, Myo, myocarditis, probable coronary embolus, Trauma, blunt chest trauma.

malities and for quantification of ejection fraction.[27]

Results

We identified 17 children (six boys, 11 girls) with typical electrocardiographic features of myocardial infarction at our hospital between February 1979 and February 1989 (table 1). Those with myocardial infarction after cardiac surgery were excluded.

Age at diagnosis ranged from two months to 12 years, with 14 patients (82%) being diagnosed at the age of 2 years or younger. Twelve patients (71%) presented with dyspnoea as the primary symptom, accompanied by vomiting or poor feeding. Two patients presented with out-of-hospital cardiac arrest (one later died), one had features of Kawasaki disease and an abnormal electrocardiogram, and two older children presented with chest pain.

The myocardial infarction was in the territory of the left coronary system in 15 of the 17 children, including the eight who died, and in the area supplied by the right coronary artery in two.

Table 2 shows the causes of myocardial infarction in this group of children. Anomalous left coronary artery arising from the pulmonary artery (35%) and Kawasaki disease (29%) accounted for most cases.

SURVIVORS

Nine patients aged from two months to 12 years at the time of myocardial infarction were alive 5 (3) (range 1–10) years after infarction. All were symptom free and were active participants in appropriate pastimes for their age. One patient (case 6) was taking cardiac medication (captopril, digoxin, and frusemide). Three patients were taking aspirin after Kawasaki disease.

Four children had open heart surgery after diagnosis. Three had surgical reimplantation of an anomalous left coronary artery to aorta. One patient with congestive cardiac failure refractory to medical treatment had resection of left ventricular aneurysm and repair of mitral valve three years after a post-traumatic coronary occlusion with infarction.

Table 3 summarises the investigations. Chest *x* rays were normal in two patients (patients 4 and 9) and showed mild cardiac enlargement in the other seven children. No *x* rays showed evidence of pulmonary venous congestion or interstitial oedema. Electrocardiography showed a pattern typical of past infarction in all the children.

The size of the infarct was assessed by dipyridamole thallium-201 myocardial scintigraphy in seven patients (one patient lives in rural New South Wales and was not able to have a thallium scan and one refused the test). All showed fixed perfusion defects of varying size consistent with scar tissue from past myocardial infarction.

Left ventricular function was assessed in all survivors by echocardiography or radionuclide gated heart pool scans or both. Left ventricular ejection fractions ranged from 21% to 66%, with most having ejection fractions <50%. Three children had mild mitral regurgitation. Wall motion abnormalities were detected and were concordant on echocardiograms and thallium scans. The echocardiogram did not show apical dyskinesis well. Mural thrombus was not detected in any patient.

Exercise capacity was assessed by formal

Table 2 Causes of childhood myocardial infarction

Disease	*Survivors*	*Non-survivors*	*Total (%)*
Anomalous origin of left coronary artery from pulmonary artery	3	3	6 (35)
Kawasaki disease	4	1	5 (29)
Myocarditis-probable coronary embolus	1	1	2 (12)
Blunt chest trauma	1	—	1 (6)
Hypertension	—	1	1 (6)
Intimal fibrosis of coronary artery	—	1	1 (6)
Absent, thrombosed, or embolised left coronary artery	—	1	1 (6)

Table 3 Follow up investigation in survivors of paediatric myocardial infarction

Case	*Age at follow up*	*Thallium scan*	*Gated LVEF (%)*	*Heart pool scan wall motion*	*Holter monitoring*
1	10½ yr	Fixed defect in posteroinferior wall	64	Area of hypokinesis in high posterior wall	Normal
2	2 yr 10 mnth	Thinning of anteroseptal area	66	Normal	Normal
3	7 yr 9 mnth	—	—	—	—
4	2 yr 10 mnth	Mild fixed apical defect	52	Moderate apical hypokinesis	Normal
5	6 yr	Fixed defect in anteroseptal wall	41	Moderate anteroseptal hypokinesis	Normal
6	4½ yr	Fixed anteroseptal and lateral wall defects	23	Anteroseptal and lateral wall akinesis	Normal
7	4½ yr	Fixed anteroseptal defect	21	Anteroseptal hypokinesis; apical dyskinesis	Run of 4 VEs at 90/min, otherwise normal
8	17 yr	—	47	Anterior wall hypokinesis	Normal
9	13 yr	Fixed anteroseptal defect	31	Anteroapical akinesis	Normal

LVEF, left ventricular ejection fraction, VEs, ventricular extrasystoles

exercise stress testing (five patients), or history and direct observation (in three patients who were too young to attempt formal exercise testing and in one patient who lived too far from a suitable exercise testing facility). Exercise capacity was ≥80% of that predicted in all patients formally tested, with normal pulse and blood pressure response. None developed chest pain, dyspnoea, or electrocardiographic changes suggestive of ischaemia.

Twenty four hour Holter monitoring was performed in eight patients (but not in one who lived in rural New South Wales). This was normal in seven patients and showed minor abnormality only in one (four consecutive ventricular extrasystoles at a rate of 90 beats per minute but otherwise normal). There were no episodes of palpitation, syncope, or out-of-hospital cardiac arrest in any patients.

DEATHS

Eight children died. All had extensive infarction of the left ventricle demonstrated by left ventriculography (two patients) or necropsy (six patients). Two children had undergone surgical repair for anomalous coronary artery.

Six children died within six months of diagnosis. Death was from cardiogenic shock, intractable heart failure or at the time of cardiac catheterisation (one patient) or surgery (one patient). Two children had longer survival times (16 months, three years), succumbing to intractable heart failure despite maximum medical treatment. There were no cases of late sudden death.

Discussion

Acute myocardial infarction is a rare cause of morbidity and mortality in childhood. We have identified 17 children seen at our hospital with myocardial infarction over a 10 year period. Mortality was high (47%) and generally occurred within 6 months of diagnosis. Excellent cardiovascular fitness and an absence of serious arrhythmia were found in survivors, even in the presence of significant left ventricular dysfunction. There were no cases of sudden out-of-hospital death. In this series, however, the number of survivors was small and there was a variety of diagnostic categories. It is therefore difficult to make authoritative conclusions about the late incidence of arrhythmia and sudden death after myocardial infarction in childhood.

There has been little information on paediatric myocardial infarction. Atherosclerosis, the most common predisposing lesion in adult myocardial infarction, is exceedingly rare in the paediatric population.[28] Chest pain, the most frequent symptom of myocardial ischaemia and infarction in adults, cannot be reported by neonates or infants. Therefore not only is the prevalence of myocardial infarction in children low but clinical detection of the condition may be difficult.

The diagnosis of myocardial infarction in children was made by electrocardiography supplemented by echocardiography and cardiac catheterisation. Electrocardiography is not 100% sensitive for myocardial infarction,[29 30] and so we may have underestimated the number of children with myocardial infarction.

There are many reported causes of myocardial infarction in childhood. In our series, anomalous origin of left coronary artery from the pulmonary artery and Kawasaki disease were the commonest causes. Myocarditis has been reported to cause both segmental cardiac necrosis mimicking myocardial infarction[31] and coronary occlusion with "true" myocardial infarction. The presumed mechanism of the latter is either coronary arteritis with thrombosis or coronary embolism from left ventricular thrombus, which we believe was the mechanism in our two patients. Blunt chest trauma has been reported to cause myocardial infarction secondary to traumatic coronary occlusion.[11 32] Other causes include intimal irregularities with in situ coronary thrombosis,[33] in utero paradoxical embolus,[8] severe cyanosis,[14] perinatal asphyxia,[34 35] and generalised arterial calcification of infancy.[15]

Mortality was high (47%) in our series. Late diagnosis in children because symptoms are not reported means that appropriate treatment is often not given immediately after acute myocardial infarction.[36] Anomalous origin of left coronary artery presenting in infancy has a high mortality in all series,[37–39] because ischaemia or infarction affects a large proportion of left ventricular muscle. The high incidence of severe cardiac failure in our patients reflects the generally large infarcts. This was confirmed at necropsy in six of the eight non-survivors.

In 1969, Imrich Bor analysed 29 cases of childhood myocardial infarction identified from necropsy files between 1945 and 1960.[9] The average age of this patient group was five years, and only one of 29 patients survived more than four months after diagnosis.

Two (12%) of our 17 cases presented with cardiac arrest, which may have been caused by early ventricular arrhythmia. This is similar to the finding of Adgey *et al* in adults, who found ventricular arrhythmias in 11·5% of 284 patients within 24 hours of the onset of myocardial infarction.[40]

There have been no series analysing long term follow up in survivors of childhood myocardial infarction. In 1986 Nakano *et al* identified 11 patients with myocardial infarction after Kawasaki disease, of whom two died.[41] The diagnosis was made by electrocardiography and echocardiography. In 1986 Kato *et al* identified the clinical and laboratory features of cardiac disease in the acute phase of Kawasaki disease in 195 patients from 151 major hospitals in Japan; however, follow up data beyond the acute phase are not provided.[42]

We followed nine survivors of paediatric myocardial infarction from one to 10 years. Some had had large infarcts, with left ventricular ejection fractions of less than 25% and large areas of akinetic ventricular wall, whereas others had small infarcts with minimal left ventricular dilatation. The striking feature was that all nine were symptom free, only one needed cardiac medication, and all had excellent exercise capacity both on history and formal testing.

This good exercise tolerance has several explanations. Firstly, children have healthy peripheral vessels, with high compliance, low resistance, and optimal myocardial/vascular coupling.[43] This may lower afterload, which has been shown to improve left ventricular remodelling and ejection fraction in adults after myocardial infarction.[44] Second, the non-infarcted myocardium should be completely healthy in children. Third, respiratory efficiency and reserve provides for considerable exercise capacity in children, which would be better than respiratory reserve in adults with myocardial infarction, many of whom have smoked heavily. Fourth, evidence from survivors of anomalous left coronary artery suggested a considerable capacity for recovery of myocardial function in children after an ischaemic insult.[45] A combination of these factors may account for the observed cardiovascular fitness of these children after myocardial infarction.

In contrast with adult series there were no instances of late cardiac arrest or sudden death in our series. Studies of adults who leave hospital after a first myocardial infarction suggest a five year mortality of approximately 25% with over half of these deaths being sudden,[46 47] and with many occurring in the first 12 months after infarction.[48]

The absence of sudden cardiac death in children after myocardial infarction in our series is difficult to explain. The young myocardium may be less prone to the development of re-entry circuits after infarction if there is less pre-existing disease of ventricular muscle. Furthermore, in infants and children good collateral blood flow in the myocardium might protect peri-infarctional ischaemic areas. Patients with Kawasaki disease may, however, prove to have poor coronary flow reserve because of coronary artery scarring.[49]

In our series no children surviving myocardial infarction had frequent ventricular extrasystoles on 24 hour electrocardiogram recordings, including those with a left ventricular ejection fraction of $< 40\%$. This places them in a low risk group for late ventricular arrhythmias. In adults with myocardial infarction who survive long enough to be discharged from hospital 40–50% have frequent or multiform ventricular extrasystoles on single 24 hour electrocardiogram recordings in the months after myocardial infarction.[50–52]

We reviewed data on 17 cases of non-operative paediatric myocardial infarction over a 10 year period. Eight children died, most of them less than six months after diagnosis, and all had large left ventricular infarcts. There were no cases of sudden out-of-hospital death. Nine survivors are currently symptom free with good exercise tolerance and no or only minor abnormalities on 24 hour electrocardiogram recordings.

1 Stryker WA Coronary occlusive disease in infants and in children. *Am J Dis Child* 1946,71·280–300

2 Host NB, Hasselbalch H, Feldt-Rasmussen B Myocardial infarction before the age of 20 is rare [Letter] *Eur J Haematol* 1988,41 511

3 Yanagisawa M, Kobayashi N, Matsuya S. Myocardial infarction due to coronary thromboarteritis following acute mucocutaneous lymph node syndrome in an infant. *Pediatrics* 1974,54 277–81.

4 Radford DJ, Sondheimer HM, William GJ, Fowler RS Mucocutaneous lymph node syndrome with coronary artery aneurysm *Am J Dis Child* 1976,130 596–8

5 Kegel SM, Dorsey TJ, Rowen M, Taylor WF. Cardiac death in mucocutaneous lymph node syndrome *Am J Cardiol* 1977,40 282–6

6 Kato H, Ichinose E, Yoshioka F, *et al* Fate of coronary aneurysms in Kawasaki disease serial coronary angiography and long-term follow-up study *Am J Cardiol* 1982,49·1758–66

7 Menahem S, Venables AW. Anomalous left coronary artery from the pulmonary artery a 15 year sample *Br Heart J* 1987,58.378–84

8 Bernstein D, Finkbeiner WE, Soifer S, Teitel D. Perinatal myocardial infarction: a case report and review of the literature *Pediatr Cardiol* 1986,6.313–7

9 Bor I Myocardial infarction and ischaemic heart disease in infants and children. *Arch Dis Child* 1969,44·268–81

10 Wroblewska-Kuluzewska M, Wojcicka-Urbanska B A case of myocardial infarction in an 11-year-old girl with myocarditis. *Paediatr Pol* 1986,61 735–9

11 Parmley LF, Manion C, Mattingly TW Nonpenetrating cardiac trauma *Circulation* 1958,18.371–96

12 Jones FL Jr. Transmural myocardial necrosis after nonpenetrating cardiac trauma. *Am J Cardiol* 1970,26 419–22

13 Courtemanche DJ, Firth CE, Onyet J Myocardial infarction in a child with salmonella enterocolitis *Paediatr Cardiol* 1986,6.279–81.

14 de Moor MMA, Vosloo SM, Human DG Myocardial infarction in a neonate with cyanotic congenital heart disease. *Pediatr Cardiol* 1986,6 219–21

15 Sholler GF, Yu JS, Dale PM, Hawker RE, Celermajer JM, Kozlowski K. Generalised arterial calcification of infancy. three case reports, including spontaneous regression with long term survival *J Pediatr* 1984;105·257–60.

16 Borow K. An integrated approach to the noninvasive assessment of left ventricular systolic and diastolic performance In St John Sutton M, Oldershaw P, eds *Textbook of adult and paediatric echocardiography and Doppler*. Oxford· Blackwell Scientific Publications, 1989 98–119.

17 Bigger JT Jr, Reiffel JA, Coromilas J Ambulatory electrocardiography. In Platia EV, ed *Management of cardiac arrhythmias* Philadelphia JB Lippincott, 1987 36–61

18 Godfrey S. Exercise and pulmonary function In. Anderson RH, Macartney FJ, Shinebourne EA, Tynan M, eds *Paediatric cardiology* New York Churchill Livingstone, 1987.395–420.

19 Cumming GR, Friesen W Bicycle ergometer measurement of maximal oxygen uptake in children *Can J Physiol Pharmacol* 1967,45:937–46

20 Anderson SD, Godfrey S. Cardiorespiratory response to treadmill exercise in normal children *Clin Sci* 1971;40:433–42

21 Sheffield LT. Exercise stress testing. In Braunwald E, ed.

Heart disease. a textbook of cardiovascular medicine Philadelphia WB Saunders, 1988:223–41

22 Weber KT, Janicki JS. Cardiopulmonary exercise testing In: Weber KT, Janicki JS *Cardiopulmonary exercise testing*. Philadelphia. WB Saunders, 1986 1–22.

23 Josephson MA, Brown BG, Hecht HS, Hopkins J, Pierce CD, Peterson RB Noninvasive detection and localization of coronary stenosis in patients comparison of resting dipyridamole and exercise thallium-201 myocardial perfusion imaging *Am Heart J* 1982,102:1008–18

24 Leppo J, Boucher CA, Okada RD, Newell JB, Strauss HW, Pohost GM. Serial thallium-201 myocardial imaging after dipyridamole infusion: diagnostic utility in detecting coronary stenosis and relationship to regional wall motion. *Circulation* 1982;66.649–57

25 Rigo P, Beck LC, Griffith LSC, *et al* Influence of coronary collateral vessels on the results of thallium-201 myocardial stress imaging *Am J Cardiol* 1979;44 452–62.

26 Srivastava SC, Chervu LR Radionuclide-labelled red blood cells current status and future prospects. *Semin Nucl Med* 1984,14.68–82.

27 Hutton BF, Cormack J, Fulton PR A software package for the analysis of gated cardiac blood pool studies. *Australas Phys Eng Sci Med* 1982;5.128–30

28 Neufeld HN, Blieden LC. Coronary artery disease in children. *Prog Cardiol* 1975;4 119–49

29 Sullivan W, Vlodaver Z, Tuna N, *et al* Correlation of electrocardographic and pathologic findings in healed myocardial infarction. *Am J Cardiol* 1978;2:724–32.

30 Levine HD, Phillips C. An appraisal of the newer electrocardiography: correlation in one hundred and fifty consecutive autopsied cases. *N Engl J Med* 1951,245.833–42.

31 Tsukada K, Takemura N, Itho K, *et al* Myocarditis with myocardial infarction like findings in a 3-year old girl. *Jpn Circ J* 1986,50.1275–9

32 Kahn JK, Buda AJ Long-term follow-up of coronary artery occlusion secondary to blunt chest trauma. *Am Heart J* 1987;113·207–10

33 Gault MH, Usher R. Coronary thrombosis with myocardial infarction in a newborn infant. clinical electrocardiographic and post-mortem findings. *N Engl J Med* 1968;263.379–82

34 Brown NJ Myocardial infarction in the newborn [Abstract] *Arch Dis Child* 1974,49 494

35 Kilbride H, Way GL, Mersenstein GB, Winfield JM Myocardial infarction in the neonate with normal heart and coronary arteries *Am J Dis Child* 1980;134 759–62

36 Burtt DM, Pollack P, Bianco JA Intravenous streptokinase in an infant with Kawasaki disease complicated by acute myocardial infarction. *Pediatr Cardiol* 1986;6·307–11

37 Vouhe PR, Baillot-Vernant F, Trinquet F, *et al* Anomalous left coronary artery from the pulmonary artery in infants Which operation? When? *J Thorac Cardiovasc Surg* 1987,94·192–9

38 Keith JD The anomalous origin of the left coronary artery from the pulmonary artery. *Br Heart J* 1959,21 149–61.

39 Wesselhoeft H, Fawcett JS, Johnson AL. Anomalous origin of the left coronary artery from the pulmonary trunk. *Circulation* 1968;38:403–25.

40 Adgey AAJ, Allen JD, Geddes JS, *et al* Acute phase of myocardial infarction *Lancet* 1971,ii.501–4.

41 Nakano H, Saito A, Ueda K, Nojima K Clinical characteristics of myocardial infarction following Kawasaki disease: report of 11 cases. *J Pediatr* 1986,108 198–203

42 Kato H, Ichinose E, Kawasaki T Myocardial infarction in Kawasaki disease: clinical analyses in 195 cases *J Pediatr* 1986;108.923–7

43 O'Rourke M *Arterial function in health and disease* New York Churchill Livingstone, 1982:153–70, 185–96.

44 Sharpe N, Smith H, Murphy J, Hannan S. Treatment of patients with symptomless left ventricular dysfunction after myocardial infarction. *Lancet* 1988,i.255–9

45 Rein AJJT, Cohan SD, Parness IA, Sanders SP Regional and global left ventricular function in infants with anomalous origin of the left coronary artery from the pulmonary trunk preoperative and postoperative assessment *Circulation* 1987,75·115–23.

46 Norris RM, Caughey DE, Mercer CJ, Scott PJ Prognosis after myocardial infarction Six year follow-up *Br Heart J* 1974,36 786–90.

47 Kannel WB, Sorlie P, McNamara P. Prognosis after initial myocardial infarction· the Framingham study *Am J Cardiol* 1978;42 202–9

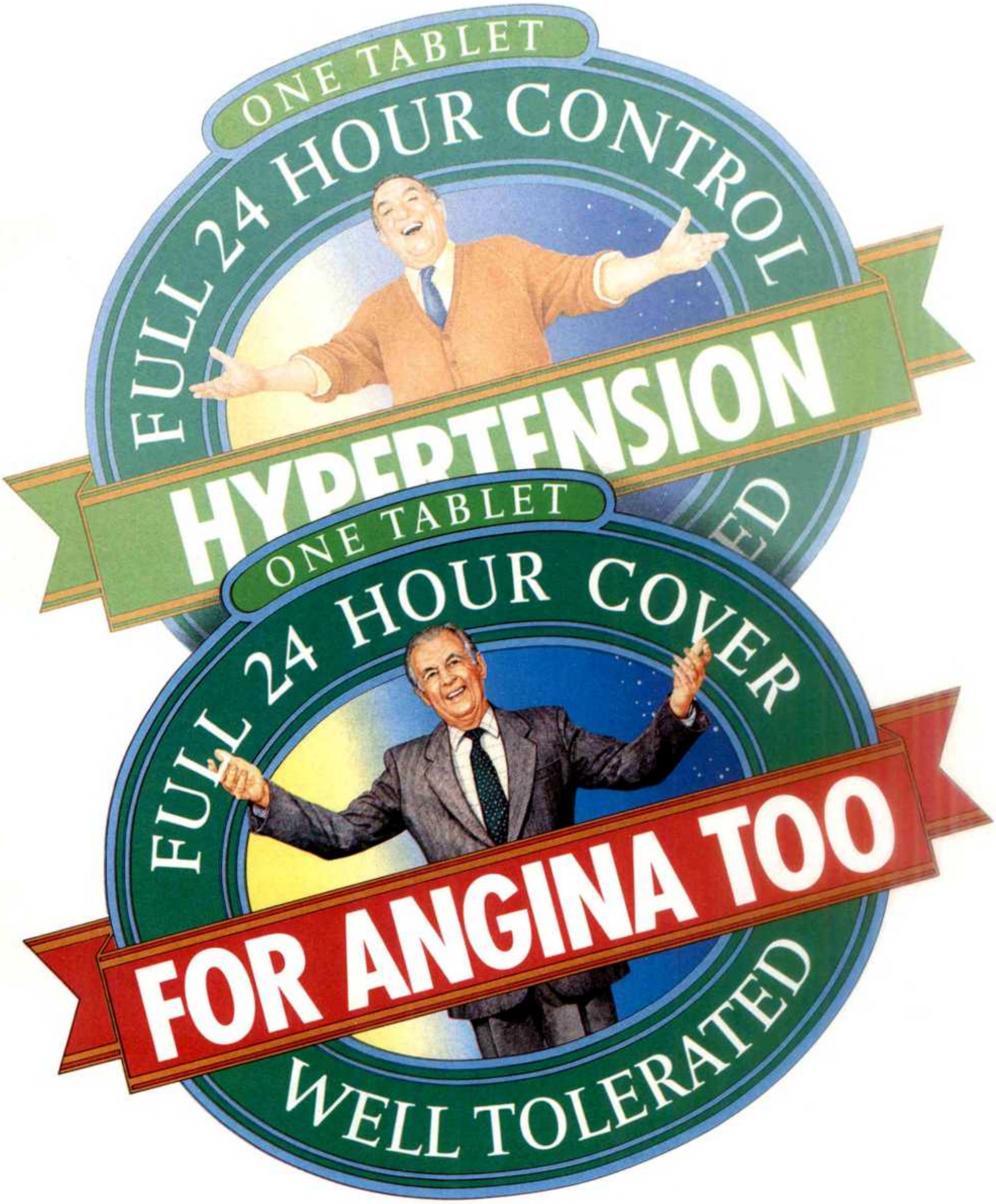
48 Bigger JT, Heller CA, Wenger TL, Weld FM. Risk stratification after acute myocardial infarction *Am J Cardiol* 1978;42 202–9

49 Spevak PJ, Newburger J, Keane J, Selwyn A, Takahashi M Reactivity of coronary arteries in Kawasaki syndrome. an analysis of function [Abstract] *Am J Cardiol* 1987;60 640

50 Kleiger RF, Martin TF, Miller JP, *et al* Ventricular tachycardia and ventricular extrasystoles during the late recovery phase of myocardial infarction [Abstract]. *Am J Cardiol* 1974,33 149

51 Van Durme JP, Pannier RH. Prognostic significance of ventricular dysrhythmias 1 year after myocardial infarction [Abstract] *Am J Cardiol* 1976,37·178.

52 Kostis JB, Byington R, Friedman IM, *et al*. Prognostic significance of ventricular ectopic activity in survivors of acute myocardial infarction. *J Am Coll Cardiol* 1987;10:231–42.



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References

1. Data on file. In trials LIPOSTAT demonstrated an LDL-cholesterol reduction of up to 34% from baseline values (after 8 weeks, 40 mg nightly).

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Influence of physical exercise on serum digoxin concentration and heart rate in patients with atrial fibrillation

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Abstract

Heart rate and serum digoxin concentration in eight patients with atrial fibrillation were studied at rest and during exercise when initial serum digoxin concentrations were zero and at low and high therapeutic values. Eight patients with ischaemic heart disease and in sinus rhythm were studied for comparison. Though the serum digoxin concentration decreased significantly during exercise, the absolute reduction in heart rate was the same at rest and during exercise in patients with atrial fibrillation. Compared with the control patients in sinus rhythm, the heart rate in patients with atrial fibrillation was not adequately controlled during exercise by any serum digoxin concentration tested despite a reduction in heart rate with increasing digoxin concentration. The effects of digoxin on heart rate regulation in atrial fibrillation are complex and include direct effects on the myocardium as well as indirect effects mediated by modulation of the autonomic nervous system; the present results indicate that the drug is not displaced from the target organs by decreasing serum concentrations during exercise.

In atrial fibrillation, because the demands on the filter function of the atrioventricular node are highly unphysiological, the effect of digoxin on heart rate during exercise is not adequate.

Digitalis is used to control the ventricular rate in patients with atrial fibrillation. Though it is effective at rest it may not prevent excessive increases in heart rate during exercise.[1–3] One possible explanation for this is that the pharmacokinetics of digoxin change during exercise. Serum digoxin concentration decreased during exercise in several studies.[4–6] This decrease has been shown to be related to an increased binding of digoxin to skeletal muscle during exercise.[4] The mechanism underlying this finding probably involves an increased digoxin binding as a consequence of an increased Na-K ATPase activity.[7] The digoxin concentration in cardiac muscle in patients with a high heart rate caused by atrial fibrillation was higher than in patients with a lower heart rate in sinus rhythm.[8] Because most of the digoxin is bound to skeletal muscle, a redistribution of digoxin during exercise might influence the amount of digoxin in other tissues. In fact a shift of digoxin from the erythrocytes to exercising skeletal muscle has been confirmed.[5] Whether digoxin shifts from the target organs to the skeletal muscle during exercise is not known, and such a shift is not easy to measure directly in humans. We investigated the effect of digoxin on heart rate in patients with atrial fibrillation to see whether an exercise induced decrease in serum digoxin concentration was followed by an impaired heart rate reduction.

Patients and methods

We studied eight men (mean age 53·3 (27–61) years; weight 82·1 (67–101) kg) with atrial fibrillation. All had experienced atrial fibrillation for at least six months. The aetiology of atrial fibrillation was ischaemic heart disease in five, previous cardiac constriction in one, and lone atrial fibrillation in two cases. Patients with clinical or echocardiographic features of valvar heart disease were excluded. None had clinical or radiological evidence of congestive heart failure. None had angina pectoris. All were normotensive, had normal results of thyroid function tests, and normal serum electrolyte concentrations. None was taking medication other than digoxin.

For comparison we studied eight men (mean age 53·3 (39–62) years; weight 77·1 (65–90) kg) with ischaemic heart disease in sinus rhythm. The diagnosis of ischaemic heart disease was based upon previous myocardial infarction. None had clinical or radiological signs of congestive heart failure. None had angina pectoris. All were normotensive and had normal thyroid function tests and serum electrolyte concentrations. No medication was given for one week before the study.

Patients with atrial fibrillation performed three series of exercise tests at intervals of two weeks. The dosage of digoxin was varied in an attempt to obtain three different serum digoxin concentrations: zero and low and high within therapeutic range (0·6–2·6 ng/ml). Doses to be given to each patient were determined by reference to the patient's maintenance dose and serum concentration before the trial. To control for the development of tolerance to the actions of digoxin during the study[9] the order of treatments was randomised. Dose schedules were kept constant for at least 10 days before each exercise test. Serum digoxin concentrations were analysed in triplicate with a commercial radioimmunoassay (Diagnostic Products). The coefficient of variation of the analysis was 2·8% at a mean value of 0·6 ng/ml and 2·0% at a mean value of 1·8 ng/ml.

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Control patients in sinus rhythm performed one series of exercise tests.

On each study day the patient did three bicycle tests at increasing workloads (25 W, 50 W, and 75 W). Each exercise test lasted 20 minutes and was followed by a one hour supine rest period. Blood samples were drawn and heart rates recorded every five minutes during the exercise periods and every 15 minutes during the resting periods. To take account of the considerable variation of heart rate in atrial fibrillation, heart rates were recorded over one minute at the end of each period.

Analysis of variance with repeated measures was used to compare changes in serum digoxin concentration at rest and during exercise. The changes in heart rate and blood pressure were analysed by two way analysis of variance, while the comparisons with the controls were evaluated by one way analysis of variance plus Dunnett's test.[10] When $p < 0{\cdot}05$ the difference was regarded as significant.

The study was approved by the regional scientific ethics committee.

Results

SERUM DIGOXIN CONCENTRATIONS

Figure 1 shows the mean (SEM) serum digoxin concentration during rest and during exercise. The mean initial value was 0·87 (0·10) ng/ml at low digoxin doses and 1·98 (0·22) ng/ml at high digoxin doses. In both groups serum digoxin concentration decreased significantly at each workload ($p < 0{\cdot}01$) and returned almost to the initial value after an hour's rest. The decrease in serum digoxin concentration depended on workload ($p < 0{\cdot}05$) and was directly proportional to the initial serum digoxin concentration ($r = 0{\cdot}92$, $p < 0{\cdot}01$ at low digoxin concentration and $r = 0{\cdot}91$, $p < 0{\cdot}01$ at high digoxin concentration).

HEART RATE DATA

Figure 2 shows heart rates at rest and during exercise at zero, low, and high serum digoxin concentration in patients with atrial fibrillation compared with control patients in sinus rhythm. In patients with atrial fibrillation, ventricular rates at rest and at all levels of exercise decreased with each increment in digoxin concentration ($p < 0{\cdot}05$), though no exact correlation between serum digoxin concentration and heart rate reduction was shown. As indicated by the parallel course of heart rate curves from patients with atrial fibrillation (fig 2) the absolute reduction in heart rate was similar at rest and during exercise. The patients with atrial fibrillation showed considerable variability in heart rate, but all patients retained their own characteristic rate pattern at various digoxin concentrations. Compared with the control group, however, only the heart rate at rest was sufficiently controlled whereas all levels of exercise caused a significant increase in heart rate ($p < 0{\cdot}05$ at 25 W and 50 W, $p < 0{\cdot}01$ at 75 W), presumably because of a greater susceptibility to physical activity in atrial fibrillation. Figure 3 shows the increase in heart rates with increasing workload and the lack of association with serum digoxin concentration.

LOG CONCENTRATION-RESPONSE RELATIONS

Because the increase in heart rate and reduction in serum digoxin concentrations were both related to workload, log concentration-response relations were evaluated at each workload separately. We found no relation between

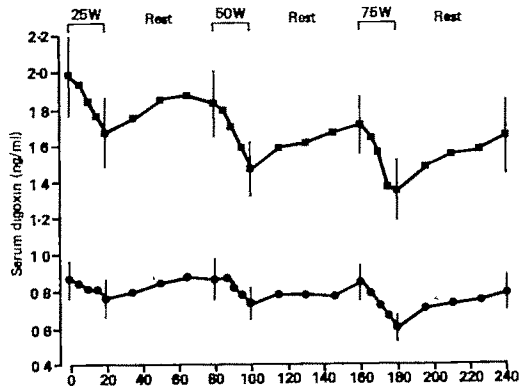

Figure 1 Serum digoxin concentration (mean (SEM)) (at high and low therapeutic concentrations) at rest and during exercise.

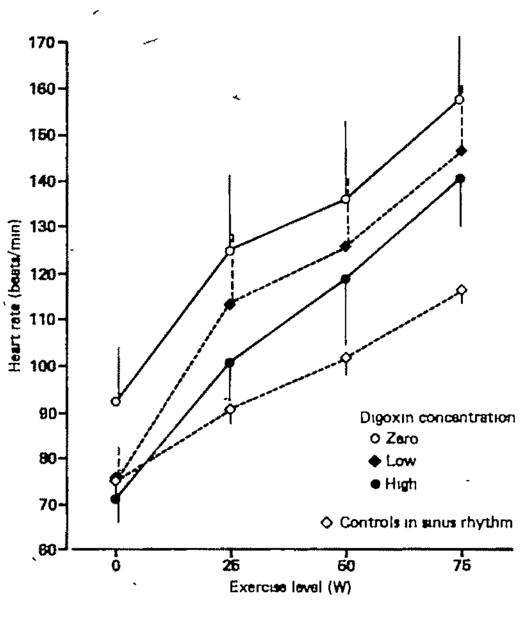

Figure 2 Heart rates (mean (SEM)) at rest and during exercise in patients with atrial fibrillation at zero, low, and high digoxin concentration. Heart rates from control patients in sinus rhythm are shown for comparison.

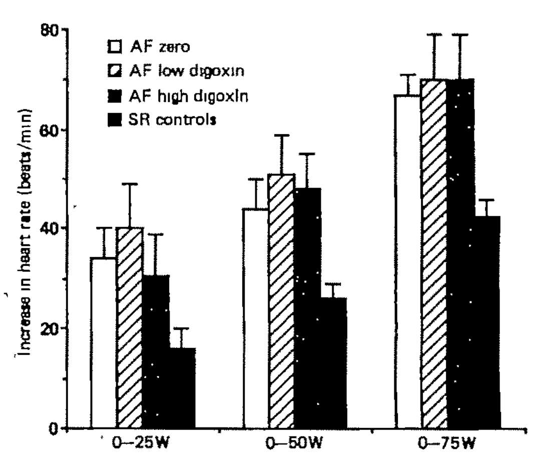

Figure 3 Increase in heart rate (mean (SEM)) from rest to 25 W, 50 W, and 75 W respectively in controls with sinus rhythm and in patients with atrial fibrillation at zero, low, and high digoxin concentration. AF, atrial fibrillation; SR, sinus rhythm.

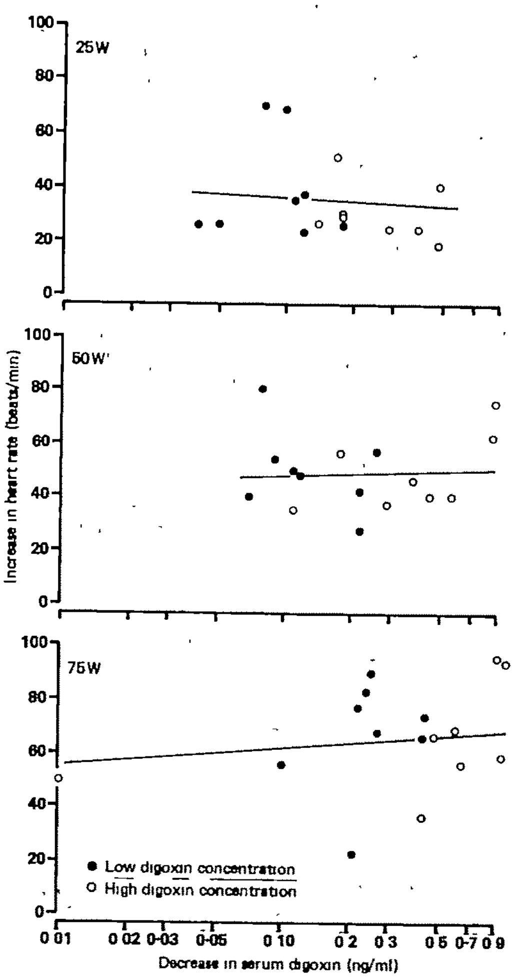

Figure 4 Relation between increase in heart rate and decrease in serum digoxin concentration in patients with atrial fibrillation at 25 W, 50 W, and 75 W exercise.

increase in heart rate and decrease in serum digoxin concentration (r = −0·30, NS at 25 W, r = 0·25, NS at 50 W, and r = 0·35, NS at 75 W) (fig 4).

HAEMODYNAMIC DATA

Changes in mean blood pressure during exercise were not affected by digoxin.

Discussion

The results of the present study confirm the findings of previous studies[1-3] that digoxin was not able to abolish the excessive increases in heart rate during exercise in atrial fibrillation. Our results also show that the increase in ventricular rate was greater in atrial fibrillation than in matched controls in sinus rhythm. The capacity of digoxin to reduce heart rate, however, did not decrease during exercise in atrial fibrillation. Mean heart rate decreased as the digoxin concentration increased and the reduction in heart rate was of equal magnitude at rest and during exercise, indicating that the increase in heart rate with exercise is the same whether or not the patients are taking digoxin. Consequently, the inadequate control of exercise heart rate in digoxin treated atrial fibrillation is rather due to the disease per se than to altered pharmacokinetics during exercise.

ROLE OF THE ATRIOVENTRICULAR NODE IN ATRIAL FIBRILLATION

The way in which the atrioventricular node scales the rapid atrial activity to a slower ventricular response in atrial fibrillation is controversial. The classic electrophysiological mechanism used to explain atrioventricular transmission includes a conduction of atrial excitation through the atrioventricular node to the His-Purkinje system and the ventricular myocardium. In normal sinus rhythm the atrioventricular node acts only as a delaying structure. The ventricular rate is directly related to the effect of stress on the firing frequency of the sinoatrial node and is not affected by autonomically induced changes in the atrioventricular nodal conduction. In atrial fibrillation the atrioventricular node is constantly bombarded by 400–600 impulses every minute. Thus atrioventricular nodal conductivity becomes the only regulating mechanism capable of controlling the ventricular rate, and the node has the characteristics of a filter.[1] The ventricular rate in atrial fibrillation is the ultimate outcome of a complex interplay of several factors, which can be grouped into three major categories: (*a*) the nature of the electrical input into the atrioventricular node, that is, the number, irregularity, and direction of atrial impulses that bombard the approaches to the atrioventricular node; (*b*) the responsiveness of the atrioventricular nodal cells and the preservation of intranodal conduction; and (*c*) the modulation of (*a*) and (*b*) by extracardiac factors such as sympathetic and parasympathetic influences and the effects of drugs. In stress or exercise, during which the sympathetic tone is increased and vagal tone decreased, atrioventricular nodal conduction is enhanced resulting in excessive impulse transmission and disproportionately high ventricular rates, far beyond the "normal" and expected acceleration produced by similar stress and exercise in sinus rhythm.

The action of the atrioventricular node as a pacemaker/oscillator electrotonically modulated by atrial activity[11-13] and also influenced by the autonomic nervous system[14 15] has recently been proposed. Conclusive evidence in support of one specific mechanism in atrioventricular transmission has yet to be presented.[16 17] Our study was not directed toward the solution of this problem and does not allow any conclusions on the mechanism(s). Our results could accord with both mechanisms. However, until the contribution of autonomic influence on atrioventricular nodal pacemaker activity in the excessive increase in ventricular rate during exercise has been clarified, the atrioventricular nodal conduction theory offers a satisfactory explanation of the atrioventricular transmission.

EFFECT OF DIGOXIN IN ATRIAL FIBRILLATION

Digoxin decreases the ventricular rate in atrial fibrillation through two synergistic pharmacological actions: (*a*) increase in the refractory period of the atrioventricular node and (*b*) decrease in the refractory period of the atrial myocardium. Both actions are mediated by direct effects on the myocardium and by indirect effects owing to a modification of both autonomic neural activity and the sensitivity of the heart to vagal and sympathetic neurotransmitters.[18,19] A decrease in the refractory period of the atrial myocardium results in more atrial impulses reaching the atrioventricular junction in a given unit of time. More atrial impulses result in a greater degree of concealed conduction[20] in the atrioventricular node and thus in a slower ventricular rate. The ventricular rhythm remains random during digitalis treatment.[18]

Our results show that digoxin is capable of exerting the same effect (evaluated as a reduction in heart rate in absolute terms) at rest and during exercise. At rest an adequate reduction in heart rate is achieved. During exercise, however, vagal tone decreases and sympathetic tone increases; this overrides the effects of digoxin.

RELATION BETWEEN SERUM DIGOXIN CONCENTRATION AND VENTRICULAR RATE RESPONSE

Several studies have shown a correlation between serum digoxin and the myocardial concentration of the drug.[8,21,22] Further, the myocardial uptake is related to the beating frequency of the heart.[8,23,24] In keeping with this the atrial concentration of digoxin was higher in patients in atrial fibrillation than in patients in sinus rhythm.[8] The relation between serum and atrial concentrations is linear in patients in sinus rhythm but not in those in atrial fibrillation.[8] Because of the various effects of digoxin the use of serum digoxin concentration in clinical practice must be based on the assumption that it reflects the degree of digitalisation of the patient and not only the relation between serum and the myocardium. The correlation between serum digoxin concentration and heart rate response is not exact.[25,26] None the less, mean falls in heart rate with increasing digoxin concentration suggest that serum digoxin concentration reflects the concentration at target organs.

The results from the present study reflect the combined effects of digoxin and do not allow us to distinguish between the direct and indirect effects. The direct effect of digoxin may be unchanged because the tendency for the myocardial digoxin concentration to decrease is offset by a concomitant increase in myocardial binding of digoxin as a secondary effect of the increased heart rate.[8]

The indirect actions of digoxin are very complex and not well understood.[19] These actions take place in the myocardium as well as in the central nervous system, the peripheral autonomic ganglia and nerves, the arterial baroreceptors, and in the carotid sinus nerves. Furthermore, several if not all of the mechanisms just mentioned are influenced by changes in the heart and circulation that modify input to the autonomic nervous system. We cannot rule out the influence of the decreased serum digoxin concentration during exercise on the indirect effects. If there is such an influence, several mechanisms may counteract the decreased indirect effect on heart rate reduction. It is impossible to unravel every aspect of the effect of digoxin on heart rate.

CLINICAL IMPLICATIONS

The results of the present study explain some of the difficulties associated with the use of serum digoxin as a guide for digoxin treatment and its failure to prevent toxic reactions in patients.[27] Because serum digoxin is affected not only by exercise but also by everyday physical activity[6,28,29] we recommend a standard rest period before blood sampling.

Our results indicate that the decrease in serum digoxin during exercise is of minor clinical importance in terms of heart rate regulation. The excessive increase in heart rate during exercise in atrial fibrillation reflects the nature of the disease.

Though an increased dose of digoxin would be of benefit even during exercise[30] it would cause only a slight improvement and increase the risk of digitalis toxicity.[31] To ensure the best possible effect and avoid reaching a toxic concentration the dose of digoxin is adjusted according to the heart rate response and serum concentration at rest. In patients with excessive increases in heart rate during exercise, digoxin alone cannot be expected to give an adequate reduction during exercise. Treatment with a calcium channel blocker ensures a better heart rate regulation both at rest and during exercise in patients with chronic atrial fibrillation.[1,32,33] Unfortunately, the superior control of exercise heart rate achieved with these agents is not associated with improved exercise endurance or "well-being" scores.[32] Further side effects are more common with calcium channel blockers in the doses needed than with digoxin or the combination of calcium channel blockers and digoxin.[32,33] Previous studies of the association between heart rate reduction and exercise capacity and symptomatic improvement during treatment with the combination of digoxin and either a calcium channel blocker or a β blocker have shown conflicting results; it is still not known whether a further reduction of heart rate during exercise is of any benefit.[32-39] When digoxin alone does not give an adequate response, we prefer the addition of a drug with an alternative mode of action such as a calcium channel blocker or a β blocker so that there is no need to approach the threshold of toxicity. Digoxin is not ideal but it is still a mainstay in the treatment of sustained atrial fibrillation.

This study was supported by grants from the Medical Research Foundation of Ringkøbing, Ribe og Sønderjylland County Hospitals, and the Danish Medical Research Council

1 Klein HO, Kaplinsky E Verapamil and digoxin: their respective effects on atrial fibrillation and their interaction. *Am J Cardiol* 1982;50·894–902

2 Goldman S, Probst P, Selzer A, Cohn K. Inefficacy of "therapeutic" serum levels of digoxin in controlling the ventricular rate in atrial fibrillation *Am J Cardiol* 1975,35·651–5.

3 Beasly R, Smith DA, McHaffie DJ. Exercise heart rates at different serum digoxin concentrations in patients with atrial fibrillation. *BMJ* 1985,290 9–11.

4 Pedersen KE, Madsen J, Kjær J, Klitgaard NA, Hvidt S. Effects of physical activity and immobilisation on plasma digoxin concentration and renal digoxin clearance. *Clin Pharmacol Ther* 1983;34:303–8

5 Joreteg T, Jogestrand T. Physical exercise and binding of digoxin to skeletal muscle—effect of muscle activation frequency. *Eur J Clin Pharmacol* 1984;27·567–70

6 Jogestrand T. Influence of everyday physical activity on the serum digoxin concentration in digoxin treated patients. *Clin Physiol* 1981,1 209–14

7 Lüllmann H, Peter T, Ziegler A Kinetic events determining

the effects of cardiac glycosides. *Trends Pharmacol Sci* 1979;1:102–6

8 Jogestrand T. Digoxin concentration in right atrial myocardium, skeletal muscle and serum in man· influence of atrial rhythm. *Eur J Clin Pharmacol* 1980;17:243–50.

9 Ford AR, Aronson JK, Graham-Smith DG, Carver JG The acute changes seen in cardiac glycoside receptor sites, 86-rubidium uptake and intracellular sodium concentrations in the erythrocytes of patients during the early phases of digoxin therapy are not found during chronic therapy: pharmacological and therapeutic implications for chronic digoxin therapy. *Br J Clin Pharmacol* 1979;8·135–42.

10 Wallenstein S, Zwecker CL, Fleiss JL. Some statistical methods useful in circulation research. *Circ Res* 1980, 47.1–9

11 Van der Tweel I, Herbschleb JN, Borst C, Meijler FL. Deterministic model of the canine atrioventricular node as a periodically perturbed, biological oscillator. *J Appl Cardiol* 1986;1 157–73.

12 Wittkampf FHM, De Jongste MJL, Lie HI, Meijler FL. Effect of right ventricular pacing on ventricular rhythm during atrial fibrillation. *J Am Coll Cardiol* 1988;11: 539–45.

13 Meijler FL, Fisch C. Does the atrioventricular node conduct? *Br Heart J* 1989;61 309–15.

14 Borst C, Meijler FL. Baroreflex modulation of ventricular rhythm in atrial fibrillation. *Eur Heart J* 1984,5:870–5.

15 Meijler FL, Kroneman J, Van der Tweel I, Herbschleb JN, Heethaar RM, Borst C Nonrandom ventricular rhythm in horses with atrial fibrillation and its significance for patients. *J Am Coll Cardiol* 1984;4:316–23

16 Kirsh JA, Sahakian AV, Baerman JM, Swiryn S. Ventricular response to atrial fibrillation. role of atrioventricular conduction pathways. *J Am Coll Cardiol* 1988;12: 1265–72.

17 Dreifus LS, Mazgalev T. "Atrial paralysis". does it explain the irregular ventricular rate during atrial fibrillation *J Am Coll Cardiol* 1988;11:546–7.

18 Meijler FL. An "account" of digitalis and atrial fibrillation. *J Am Coll Cardiol* 1985;5.60A–8A.

19 Hoffmann BF, Bigger JT. Digitalis and allied cardiac glycosides. In: Gilman AG, Goodman LS, Rall TW, Murad F, eds. *The pharmacological basis of therapeutics*. New York: Macmillan, 1980:729–60

20 Langendorf R, Pick A, Katz LN. Ventricular response in atrial fibrillation: role of concealed conduction in the AV junction *Circulation* 1965,32:69–75.

21 Härtel G, Kyllonen K, Merikallio E, Ojala K, Manninen V, Reissel P. Human serum and myocardium digoxin. *Clin Pharmacol Ther* 1976;19:153–7.

22 Gullner HG, Stinson EB, Harrison DC, Kalman SM. Correlation of serum concentrations with heart concentrations of digoxin in human subjects. *Circulation* 1974; 50:653–5

23 Lloyd BL, Taylor RR. Influence of myocardial mechanical activity and coronary blood flow on myocardial digoxin uptake *Cardiovasc Res* 1976,10·487–93.

24 Lloyd BL, Taylor RR. The effect of heart rate on myocardial oubain uptake and on the susceptibility to oubain cardiotoxicity in the dog. *Clin Exp Pharmacol Physiol* 1978,5:171–9.

25 Chamberlain DA, White RJ, Howard MR, Smith TW Plasma digoxin concentrations in patients with atrial fibrillation. *BMJ* 1970;iii.429–32.

26 Halkin H, Kleiner A, Almog S, Millman P, Tirosh M. Value of serum digoxin concentration measurement in the control of digoxin therapy in atrial fibrillation. *Isr J Med Sci* 1979,15.490–3.

27 Fogelmann AM, La Mont JT, Finkelstein S, Rado E. Fallibility of plasma digoxin differentiating toxic from non-toxin patients. *Lancet* 1971,ii.727–9.

28 Jogestrand T, Nordlander R Serum digoxin determination in outpatients—need for standardization. *Br J Clin Pharmacol* 1983,15.55–8.

29 Laursen SØ, Pedersen KE, Klitgaard NA. Influence of physical activity on plasma digoxin in hospitalised patients. *Dan Med Bull* 1987;34.115–7

30 Redfors A Digoxin dosage and ventricular rate at rest and exercise in patients with atrial fibrillation. *Acta Med Scand* 1971;190 321–33.

31 Smith TW. Digitalis. Mechanisms of action and clinical use *N Engl J Med* 1988;318.358–65.

32 Lewis R, Lakkani M, Moreland TA, McDewitt DG. A comparison of verapamil and digoxin in the treatment of atrial fibrillation. *Eur Heart J* 1987,8.148–53.

33 Roth A, Harrison E, Mitani G, *et al* Efficacy and safety of medium-and high dose diltiazem alone and in combination with digoxin for control of heart rate at rest and during exercise in patients with atrial fibrillation *Circulation* 1986;73:316–24

34 Steinberg JS, Katz RJ, Bren GB, Buff LA, Varghese PJ Efficacy of oral diltiazem to control ventricular response in chronic atrial fibrillation at rest and during exercise *J Am Coll Cardiol* 1987;9·405–11

35 Lewis R, Laing E, Moreland TA, Service E, McDewitt DG. A comparison of digoxin, diltiazem and their combination in the treatment of atrial fibrillation *Eur Heart J* 1988,9 279–83.

36 DiBianco R, Morganroth J, Freitag JA, *et al* Effects of nadolol on the spontaneous and exercise provoked heart rate of patients with chronic atrial fibrillation receiving stable doses of digoxin. *Am Heart J* 1984,108.1121–7.

37 Lang R, Klein HO, Weiss E, *et al*. Superiority of oral verapamil therapy to digoxin in the treatment of chronic atrial fibrillation *Chest* 1983,83·491–9

38 Brown RW, Goble AJ Effect of propranolol on exercise tolerance of patients with atrial fibrillation *BMJ* 1969;ii 279–80

39 David D, DiSegni E, Klein HO, Kaplinsky E. Inefficacy of digitalis in the control of heart rate in patients with chronic atrial fibrillation beneficial effect of an added beta adrenergic blocking agent *Am J Cardiol* 1979,44.1379–82

Br Heart J 1991;65:342–5

Jugular venous 'a' wave in dilated cardiomyopathy: sign of abbreviated right ventricular filling time

C H Lee, H B Xiao, D G Gibson

Abstract

***Objective*—To study the mechanisms underlying the high venous pressure often seen in patients with dilated cardiomyopathy.**

***Design*—Retrospective and prospective examination of the pattern of flow in the superior vena cava, cardiac echo-Doppler studies, and recordings of the jugular venous pulse.**

***Setting*—A tertiary referral cardiac centre.**

***Patient participants*—23 patients with dilated cardiomyopathy, all with functional mitral and tricuspid regurgitation.**

***Results*—Two patterns of venous pulse were seen: a dominant 'a' wave and 'x' descent, with systolic flow in the superior vena cava (group 1, n = 11), and a dominant 'v' wave with 'y' descent and diastolic flow in the superior vena cava (group 2, n = 12). A comparison of group 1 and group 2 showed: age (mean (SD)) 58 (12) *v* 61 (6) years, left ventricular end diastolic dimension 7·0 (0·7) cm in both groups, right ventricular short axis 3·3 (0·6) *v* 3·6 (0·5) cm and long axis 7·3 (0·5) *v* 7·1 (0·7) cm, and duration of tricuspid regurgitation 350 (65) *v* 370 (50) ms. The RR interval (550 (100) *v* 680 (80) ms) and right ventricular filling time (150 (30) *v* 290 (50) ms) were significantly shorter in group 1. In all patients in group 2 right ventricular filling time was more than 200 ms with separate E and A waves on the tricuspid Doppler echocardiogram, while in all group 1 patients it was less than 200 ms with a single summation peak. In nine patients in group 1, the right ventricular filling time was limited by prolonged tricuspid regurgitation and in the remaining two by prolonged isovolumic relaxation time (215 (80) ms), so that it was consistently significantly less than that of the left ventricle.**

***Conclusion*—In patients with dilated cardiomyopathy, right ventricular filling time may be so short that it limits stroke volume. Such patients can be recognised by a dominant 'a' wave on the jugular venous pulse. Patients in whom the right ventricular filling time was longer showed a dominant 'v' wave. Both groups can present as "congestive heart failure".**

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The jugular venous pressure is often raised in patients with dilated cardiomyopathy and this is taken to be a sign of "congestive heart failure".[1] We found that the characteristics of the venous pulse in these patients varied considerably from patient to patient. In particular, we have been struck by how frequently a dominant 'a' wave can occur in the absence of severe pulmonary hypertension or organic tricuspid valve disease. Because a dominant 'a' wave seems to reflect a specific disturbance of right ventricular filling and because its recognition may well modify treatment we examined its underlying mechanism in more detail.

Patients and methods

STUDY POPULATION

We studied 23 patients (18 men and five women, aged 43–84) with dilated cardiomyopathy (defined as a left ventricular end diastolic dimension >6·5 cm and fractional shortening less than 20%). All the patients were in sinus rhythm and had a raised jugular venous pressure. They were selected only in so far as they fulfilled these criteria and had technically satisfactory records.

M MODE AND CROSS SECTIONAL ECHOCARDIOGRAPHY

M mode echograms of the mitral valve and left ventricle were recorded with a 3·0 MHz transducer and ATL Imager Mk 300I. The left parasternal long axis view was used with the patient in the left lateral position.

Phonocardiograms and electrocardiograms were recorded simultaneously on a Honeywell recorder at a paper speed of 10 cm/s. The internal dimension of the left ventricle was measured at end diastole (that is at the onset of QRS complex on the electrocardiogram) and at end systole (at aortic closure) by the leading edge method.

The right ventricle was measured from end diastolic frames of the apical four chamber view. The short axis was measured transversely at the tip of the tricuspid valve leaflets and the long axis from the central point of the tricuspid annulus to the apex.

DOPPLER ECHOCARDIOGRAPHY

Doppler recordings were made with Doptek equipment and a 2·0 MHz transducer. Regurgitant flow across the tricuspid and mitral valves was recorded from the apex, whereas flow in the superior vena cava was measured from the right supraclavicular fossa. Simultaneous phonocardiograms and electrocardiograms were again recorded. The durations of mitral and tricuspid regurgitation were measured for each patient and the interval between two successive regurgitant signals was taken to be the filling time. Measurements were made on three cardiac cycles and the mean value obtained. The flow pattern in the superior vena cava was individually analysed in conjunction with the jugular venous pulse tracings.

JUGULAR VENOUS PULSE RECORDING

This was recorded with the patient in a semirecumbent position. A pressure transducer with a time constant of 4 seconds was used in this study. Simultaneous phonocardiograms and electrocardiograms were recorded. Where possible, the jugular venous pulse traces were superimposed on the Doppler display of flow in the superior vena cava. In patients with a dominant 'v' wave, the increase in the venous pulse above its minimum value was measured at end diastole and expressed as a percentage of the overall excursion during the cardiac cycle.

STATISTICAL ANALYSIS

Values are given as mean (SD). Differences between mean values were compared by Student's *t* test.

Results

JUGULAR VENOUS PULSE AND FLOW IN THE SUPERIOR VENA CAVA

We saw two patterns of venous pulse and flow in the superior vena cava: patients in group 1 (n = 11) had a dominant 'a' wave and 'x' descent on the jugular venous pulse (fig 1A) and systolic flow in the superior vena cava (fig 1B) whereas those in group 2 (n = 12) had a dominant jugular venous 'v' wave and 'y' descent (fig 2A) and diastolic flow in the superior vena cava (fig 2B). In group 2 the venous pressure rose mainly in diastole (83 (38)% of total excursion) in 10 of the 12 patients, and in the other two, the dominant increase was in systole.

CHARACTERISTICS OF PATIENTS ACCORDING TO VENOUS PULSE PATTERN (TABLE)

Age, left ventricular end diastolic dimension, ejection fraction, right ventricle to right atrium pressure drop, right ventricular short and long axes, and the duration of tricuspid regurgitation were similar in the two groups of patients.

The RR interval and right ventricular filling time were, however, shorter in group 1 patients ($p < 0{\cdot}01$). In all group 2 patients right ventricular filling time was > 200 ms, with E and A waves visible on the transtricuspid Doppler flow; whereas all group 1 patients had a right ventricular filling time shorter than 200 ms and a single summation peak on the tricuspid Doppler flow (fig 3A). Unlike the filling time, there was considerable overlap of RR intervals measured in group 1 and group 2) (group 1, 400–690 ms; group 2, 590–820 ms), and by itself the RR interval did not clearly distinguish them.

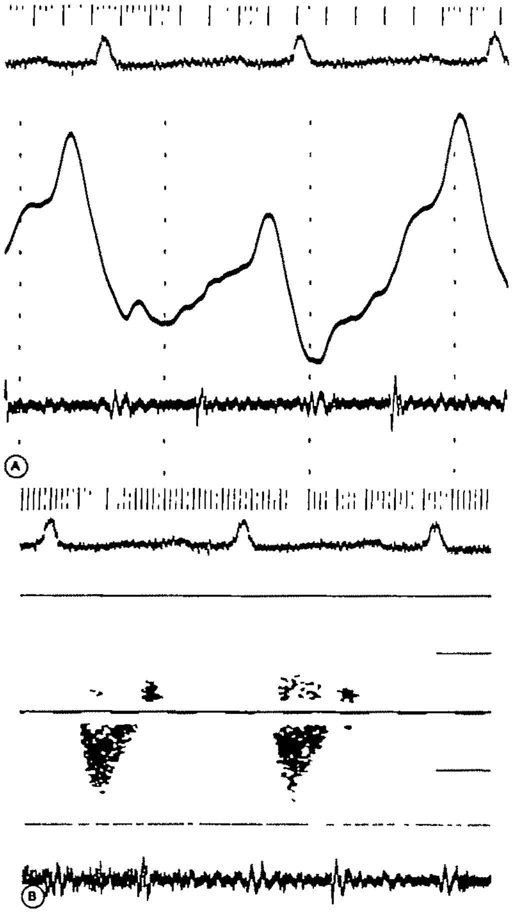

Figure 1 (A) Jugular venous pulse from a patient with dilated cardiomyopathy showing a dominant 'a' wave and 'x' descent. Note absence of 'v' wave and 'y' descent. A simultaneous phonocardiogram was recorded. (B) Simultaneous phonocardiogram and pulsed Doppler recording of flow velocity in the superior vena cava of the same patient. Downward flow towards the right atrium occurred only during ventricular systole. No flow was recorded after the second heart sound. (Doppler full scale deflection is 2 kHz.)

The right ventricular filling time was limited by prolonged tricuspid regurgitation in nine of the 11 patients in group 1 (fig 3B). In the other two patients, filling time was short because the onset of forward flow was delayed (by 55 and 110 ms) after the end of tricuspid regurgitation.

COMPARISON BETWEEN RIGHT AND LEFT SIDED FILLING CHARACTERISTICS (TABLE)

In both groups of patients tricuspid regurgitation lasted longer than mitral regurgitation. Correspondingly, the right ventricular filling time was significantly shorter than that of the left ventricle in both groups of patients (group 1, 150 (30) *v* 215 (80) ms; group 2, 290 (50) *v* 335 (60) ms, $p < 0{\cdot}05$).

Discussion

A dominant 'a' wave in the venous pulse is a striking physical sign and always needs to be explained. We found it in half of our patients

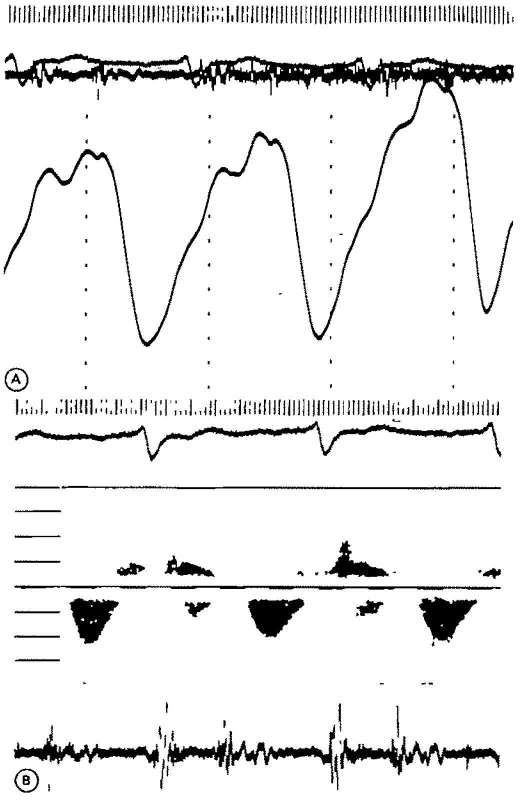

Figure 2 (A) Jugular venous pulse from another patient with dilated cardiomyopathy showing a dominant 'v' wave and 'y' descent. There was no clearly defined 'a' wave or 'x' descent. (B) Pulsed Doppler recording of flow velocity in the superior vena cava in the same patient. Downward flow was almost exclusively diastolic and followed the second heart sound on the simultaneous phonocardiogram. The third heart sound corresponded to the nadir of the flow velocity signal. (Doppler full scale deflection is 4 kHz.)

with dilated cardiomyopathy with a raised venous pressure. It seemed surprisingly common in view of how little it has been written about. Though this physical sign was well known to Mackenzie,[2] it has been overlooked and knowledge of it subsequently lost. It is not mentioned, for example, in any of the standard textbooks of cardiology.[3-6]

Patients with a dominant 'a' wave and without were indistinguishable in terms of age, left and right ventricular cavity size, or right ventricle to right atrium pressure drop as measured by continuous wave Doppler. There were two major differences: heart rate was higher (109 as against 88 beats per minute) and in particular there was no overlap in right ventricular filling time between the two groups, the mean being 150 ms in those with dominant 'a' wave and 290 ms in those without. At a rapid heart rate, right ventricular filling time was limited in most patients by the tricuspid regurgitation. Forward flow could not start until the end of the regurgitation, and it was terminated either by the succeeding ventricular systole or (in three patients) prematurely by the onset of diastolic tricuspid regurgitation associated with a prolonged PR interval. The right ventricular filling time was thus shortened and its onset delayed until after the P wave of the succeeding beat. Early diastolic and atrial flow were thus superimposed ("summated") to give a single, short pulse across the tricuspid valve. The venous pulse might therefore be described in the same way, although its timing and duration were characteristic of an 'a' wave.

We have previously described shortened filling time in patients with dilated cardiomyopathy of the left side of the heart.[7] In patients with functional mitral regurgitation the time available for forward flow is significantly less than that predicted from the period that the mitral valve cusps are separated and is limited to the interval between the pulses of regurgitation. The overall duration of the regurgitation varies little with heart rate, so that as RR interval falls, filling time becomes disproportionately shortened. When filling time drops below 200 ms the pattern of the flow velocity curve changes; separate E and A waves are lost and replaced by a single peak, often accompanied by a summation sound. The short time available for filling thus seems to limit stroke volume, suggesting an analogy with mitral stenosis, though on a temporal rather than a spatial basis. The same mechanisms seemed to be present in our patients on the right side of the heart. In patients with a dominant 'a' wave, filling time was again less than 200 ms, raising the obvious analogy with temporal tricuspid stenosis. Gibson and Wood comprehensively described the physical signs of rheumatic tricuspid stenosis.[8] They pointed out that in such patients a clinical diagnosis could be confidently based on a dominant 'a' wave in the venous pulse and the absence of a deep 'y' trough or physical signs of severe pulmonary hypertension. These signs are strikingly similar to those found in our patients with dilated cardiomyopathy and they extend the analogy between temporal and spatial atrioventricular valve stenosis.

Several other possible mechanisms might have caused the 'a' wave in our patients. The size of the right ventricular cavity was similar in the two groups of patients. The systolic pressure drop from right ventricle to right atrium was virtually identical irrespective of the pat-

Jugular venous pulse patterns and associated features (mean (SD))

Variable	*Group 1 Dominant 'a' wave (n = 11)*	*Group 2 Dominant 'v' wave (n = 12)*	*p Values*
Age (yr)	58 (12)	61 (6)	NS
RR intervals (ms)	550 (100)	680 (80)	<0·01
Left ventricular end diastolic dimension (cm)	7·0 (0·7)	7·0 (0·7)	NS
Right ventricular short axis (cm)	3·3 (0·6)	3·6 (0·5)	NS
Right ventricular long axis (cm)	7·3 (0·5)	7·1 (0·7)	NS
Left ventricular end systolic dimension (cm)	6·3 (0·8)	6·0 (0·7)	NS
Ejection fraction (%)	12 (5·4)	14 (3·9)	NS
Right ventricle–right atrium pressure drop (mm Hg)	30 (5)	30 (5)	NS
Duration of tricuspid regurgitation (ms)	350 (65)	370 (50)	NS
Right ventricular filling time (ms)	150 (30)	290 (50)	<0·01
Duration of mitral regurgitation (ms)	340 (40)	340 (30)	NS
Left ventricular filling time (ms)	215 (80)	335 (60)	<0·01

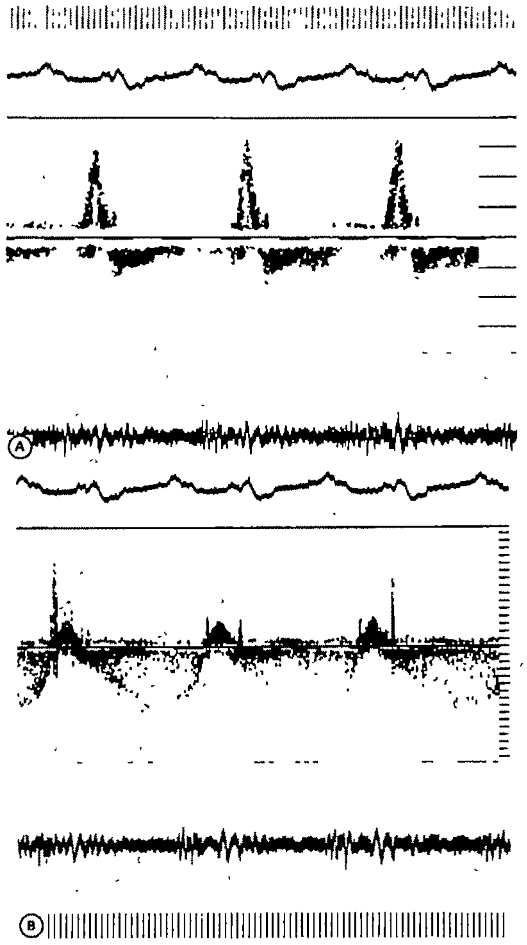

Figure 3 (A) Pulsed Doppler recording of forward tricuspid flow velocity. Overall filling time was reduced to 80 ms and occurred exclusively after the P wave of the succeeding beat. (Doppler full scale deflection is 4 kHz.) (B) Continuous wave Doppler recording showing tricuspid regurgitation signal from the same patient. PR interval was prolonged and the onset of the regurgitation was presystolic. The interval between the pulses of regurgitation corresponded to the short right ventricular filling time. (Doppler full scale deflection is 16 kHz.)

term of the venous pulse. This shows that the severity of pulmonary hypertension did not account for the dominant 'a' wave. Right ventricular diastolic function might have been impaired by primary disease or as the result of Bernheim effect from the left ventricle.[9] In patients whose heart rates were slower this dysfunction manifested itself in the characteristic way as a deep 'y' descent and dominant increase in venous pressure during diastole. A pressure increase that occurred predominantly during systole, as would be expected if tricuspid regurgitation were the mechanism, was much less frequent. This makes it unlikely that the tricuspid regurgitation was haemodynamically significant or that differences in the severity of regurgitation explained our findings. We conclude, therefore, that a dominant 'a' wave in the venous pulse in patients with dilated cardiomyopathy is not caused by primary right ventricular disease, severe pulmonary hypertension, or impaired diastolic function as the result of left side involvement, but is the direct effect of the limited time available for tricuspid inflow. "Temporal tricuspid stenosis" was therefore present in about half of our patients.

When the venous pressure is raised in patients with dilated cardiomyopathy, they are often said to be in "congestive heart failure". Though the term has never been adequately defined, heart failure is usually regarded as an undesirable state of affairs that should be treated. The standard treatment for a raised venous pressure is to administer diuretics until it falls. When filling time is limited, a normal stroke volume can only enter the ventricle if mean flow rate is increased; this requires an increase in acceleration rate at the start of filling and deceleration rate at its end. Such velocity changes require corresponding pressure gradients along the direction of flow of approximately 1 mm Hg/cm for each 1 *g* of acceleration. The pressure wave recorded in the venous pulse directly reflects the pressure changes across the valve that make this rapid filling possible. To lower venous pressure would thus be to remove a potential compensatory mechanism. It seems better either to reduce the duration of the tricuspid regurgitation or to lower the heart rate, both of which would increase filling time. This approach to treatment is quite different from that to be adopted if the venous pressure is raised by functional tricuspid regurgitation or reduced ventricular compliance. Our results show yet again that many different pathological mechanisms may be responsible for "heart failure"—a clinical diagnosis that is imprecise. It is quite possible with simple clinical skills to recognise the disturbance we have described and it can readily be confirmed non-invasively. More effective treatment is then likely to follow from more precise diagnosis.

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1 Fishberg AM The venous pressure and pulse In. *Heart failure* Philadelphia: Lea and Febiger, 1940·96–119.
2 Mackenzie J The auricular form of the venous pulse. In *The study of the pulse. arterial, venous and hepatic, and the movement of the heart*. Edinburgh: Pentland, 1902. 197–208.
3 Wenger NK, Goodwin JF, Roberts WC. Cardiomyopathy and myocardial involvement in systemic disease. In. Hurst JW, ed *The heart, arteries and veins* New York. McGraw-Hill, 1986:1181–248.
4 Shabetai R. Dilated cardiomyopathy In: Parmley WW, Chatterjee K, eds *Cardiology*. Philadelphia. Lippincott, 1987·41.1–16.
5 Littler WA Dilated cardiomyopathy. In Julian DG, Camm AJ, Fox KM, Hall RJC, Poole-Wilson PA, eds. *Diseases of the heart*. London: Bailliere Tindall, 1989:916–24
6 Wynne J, Braunwald E. The cardiomyopathies and myocarditides. In: Braunwald E, ed. *Heart disease, a textbook of cardiovascular medicine*. Philadelphia W B Saunders, 1988·1410–69.
7 Ng KSK, Gibson DG. Impairment of diastolic function by shortened filling period in severe left ventricular disease. *Br Heart J* 1989;62·246–52.
8 Gibson R, Wood P. The diagnosis of tricuspid stenosis. *Br Heart J* 1955;17·552–62.
9 Bernheim DR. De l'asystolie veineuse dans l'hypertrophie du coeur gauche. *Rev de Méd* 1910;30 785–801

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Balloon dilatation of restrictive interatrial communications in congenital heart disease

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Abstract

An adequate interatrial communication is necessary for survival in several forms of congenital heart disease. Three children are presented in whom blade atrial septostomy proved either technically impossible or failed to achieve adequate interatrial communication. In all three an adequate communication was obtained by a balloon dilatation technique similar to that used for pulmonary valve dilatation. In one critically ill infant with mitral atresia the procedure was life saving.

The survival of infants with certain congenital cardiac defects depends on the presence of an adequate interatrial communication. Such a communication is usually present at birth, but will often become restrictive with increasing age and an adequate communication will then have to be made. The Rashkind balloon septostomy procedure is usually successful in neonates,[1] but is often ineffective after the neonatal period because the thickened atrial septum is less liable to tear. The development of the Park blade septostomy catheter means that surgical atrial septectomy can now be avoided in many of these patients.[2] However, blade septostomy may prove technically impossible or result in an inadequate communication. In addition, not all cardiologists are familiar with this technique. In three children we used a balloon dilatation procedure of the atrial septum similar to that performed for pulmonary valve dilatation.

Patients and methods

The table shows the patients' details. Patient 1 had pulmonary atresia with an intact interventricular septum and a hypoplastic tricuspid valve. When he was two and a half progressive hepatic congestion due to a restrictive interatrial communication developed. Blade atrial septostomy was attempted then and again six months later. This was performed in the standard manner[2] and without complication, but resulted in minimal change in atrial pressures.

Patient 2 presented with central cyanosis, circulatory collapse, and severe respiratory distress when he was eight weeks old. The arterial pH was 7·0. After vigorous resuscitation an echocardiogram showed a univentricular heart of right ventricular morphology, mitral atresia, double outlet right ventricle, and a severely restrictive interatrial communication with thickened interatrial septum. He was transferred to the cardiac catheterisation laboratory so that an adequate interatrial communication could be created. Because of the patient's age and thickening of the interatrial septum a Rashkind balloon septostomy was not attempted. It proved impossible to manipulate a Park blade septostomy catheter through the restrictive foramen ovale to the small left atrium. However, a 4 French multipurpose catheter and guide wire could be passed to the left atrium with ease. It was, therefore, decided to perform balloon atrial septal dilatation rather than introduce the Park blade catheter by transseptal puncture.

Patient 3 had been followed since birth with a diagnosis of double outlet right ventricle and a subpulmonary ventricular septal defect. Pulmonary artery banding was performed when he was six weeks old. He did well until he was one year old when he began to tire very easily. Though only modest central cyanosis was noted at rest, crying or exertion caused considerable cyanosis. Echocardiography showed only a small atrial septal defect with left to right bowing of the atrial septum. We thought that his symptoms were in part due to poor interatrial mixing and might be improved by enlargement of the interatrial communication. Blade septostomy was performed in the usual manner without technical difficulty, but because it did not significantly change atrial pressures we attempted balloon atrial septostomy.

PROCEDURE (FIGS 1 AND 2)

A similar procedure was performed in all three patients. Patient 2 was artificially ventilated because of his critical condition; the other two were given intravenous sedation and were breathing spontaneously. After percutaneous catheterisation of the right femoral vein, right and transseptal left atrial pressures and saturations were measured with a size 4 or 5 French multipurpose catheter. With the catheter in the left atrium, the catheter was exchanged for a 0·035 or 0·038 inch guide wire over which a balloon dilatation catheter was passed (Meditech UT or DC series). The table shows the catheter and balloon sizes used. In each case, the mid-portion of the balloon was positioned at the atrial septal defect by fluoroscopy and cross sectional echocardiographic guidance. All procedures were performed with a standard length (3 cm) balloon. This provided sufficient balloon length for stabilisation of the balloon, without placement of the proximal or distal

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*Patient characteristics and results of balloon dilatation of the atrial septum**

Patient	Age	Diagnosis	Previous septostomy	Balloon diameter, length/catheter size	Haemodynamic data		Follow up
					Pre-dilatation	Post-dilatation	
1	3 yr	PA, IVS	RBS 2 days, PBS 2·5 and 3 yr	18 mm × 30 mm/9 French	RA 14 mm Hg, LA 5 mm Hg; sat LA 91%	RA 10 mm Hg, LA 10 mm Hg; sat LA 80%	Well age 6 yr, awaiting Fontan
2	8 wk	MA, DORV, IVS	Nil	8 mm × 30 mm/5 French	RA 4 mm Hg, LA 32 mm Hg; sat RA 31%, RV 40%, LA 99%	RA 4 mm Hg, LA 12 mm Hg; sat RA 64%, RV 83%, LA 98%	PAB and BHS age 4 mnth, well age 7 mnth
3	1 yr	DORV, PAB, spVSD	PBS 1 yr	15 mm × 30 mm/9 French; 20 mm × 30 mm/9 French	RA 2 mm Hg, LA 10 mm Hg; sat RA 54%, LA 97%, Ao 81%	RA 3 mm Hg, LA 5 mm Hg; sat RA 62%, LA 94%, Ao 89%	Arterial switch/VSD closure age 3 yr; well age 4 yr

*Patients 1 and 3 were breathing spontaneously in air and patient 2 was artificially ventilated in 90% oxygen.
Ao, aorta; BHS, Blalock-Hanlon septectomy; DORV, double outlet right ventricle; IVS, intact ventricular septum; LA, left atrium; MA, mitral atresia; PA, pulmonary atresia; PAB, pulmonary artery band; PBS, Park blade septostomy; RA, right atrium; RBS, Rashkind balloon septostomy; sat, oxygen saturation; spVSD, subpulmonary ventricular septal defect.

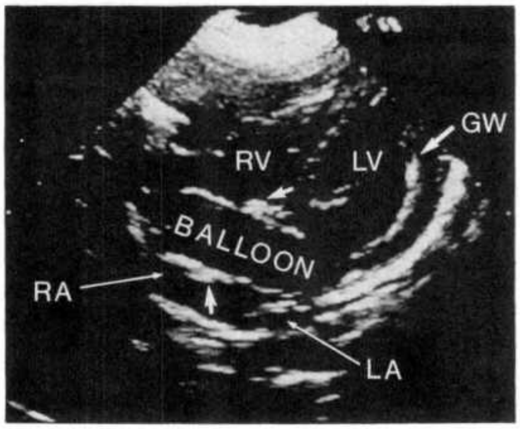

Figure 1 Cross sectional echocardiogram from patient 3. Subcostal view showing balloon positioned across the atrial septal defect during full inflation. Guide wire was visible within the left ventricle. Atrial septum was adjacent to the mid portion of the balloon (arrowed) and no waist was evident. GW, guide wire; LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.

portion of the balloon in the inferior vena cava, pulmonary vein, or across the left atrioventricular valve. When a satisfactory position had been obtained, the balloon was inflated to its maximum size with inflation pressures about equal to the manufacturer's maximum recommended inflation pressure. Deflation was started as soon as the maximum balloon diameter was obtained and the waist disappeared. Each balloon was inflated three times. In patient 3, the initial inflation of the balloon resulted in stripping of the atrial septum distally along the balloon, rather than a local dilatation and tear of the septum. When the guide wire and balloon were repositioned more distally dilatation of the atrial septal defect was satisfactory. Atrial pressures and saturations were remeasured after the three dilatations.

Results

The table shows the effect of balloon dilatation on atrial pressures. In patient 1 dilatation resulted in equalisation of phasic and mean atrial pressures with resolution of hepatic congestion. Echocardiography confirmed that the atrial septum was no longer bowed and that the atrial septal defect was enlarged. He remains well three years after the procedure and is awaiting correction by a Fontan procedure.

The second patient, who was profoundly ill at presentation, showed the greatest initial improvement after dilatation. The mean left atrial pressure was considerably reduced from 32 mm Hg to 12 mm Hg, though an 8 mm Hg interatrial gradient persisted. Saturation in the systemic ventricle increased from 40% to 83%, and his acidosis rapidly resolved. He was easily extubated within 24 hours of the procedure. The persistence of a gradient between the two atria suggested that palliation might be only temporary. He remained well for two months before signs of left atrial hypertension re-

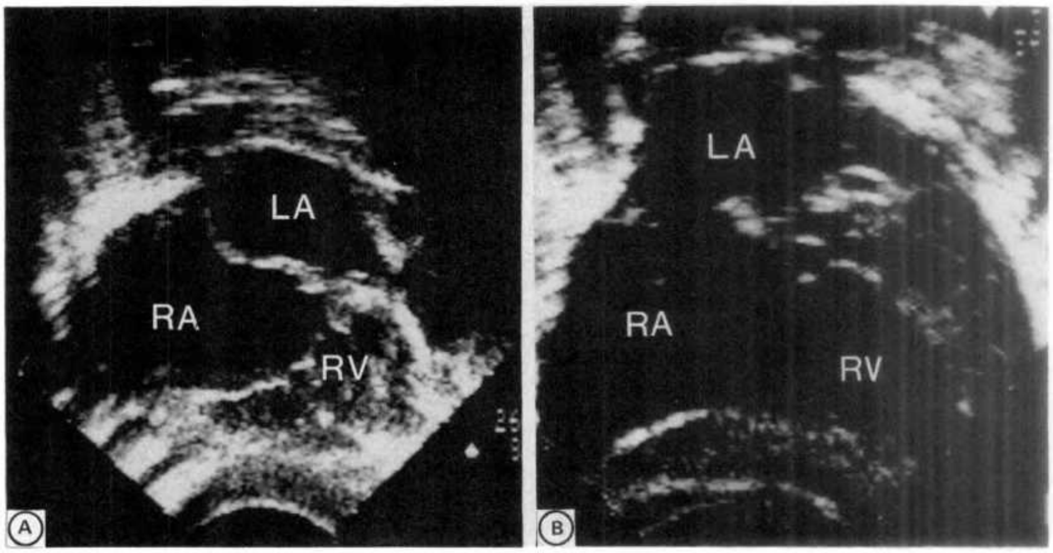

Figure 2 Subcostal cross sectional echocardiographic images of patient 2 before (A) and after (B) balloon dilatation. (A) Before dilatation the septum was tense and bowed to the right. After dilatation (B) the atrial septum was no longer bowed and a central defect with a diameter of about 8 mm had been created. LA, left atrium; RA, right atrium; RV, right ventricle.

curred. When he was four months old a Blalock-Hanlon atrial septectomy was performed at the time of pulmonary artery banding.

In the third patient with double outlet right ventricle and subpulmonary ventricular septal defect with a pulmonary artery band, the initial dilatation with a 15 mm balloon had no effect on the atrial pressures. However, after dilatation with a 20 mm balloon the mean atrial pressure gradient was reduced from 8 to 2 mm Hg. His maximum resting aortic saturation rose from 81% to 89% and his parents reported that his exercise tolerance and rate of growth had increased. An arterial switch procedure and closure of the ventricular septal defect were successful two years later when he was three years old. At operation the persistence of an interatrial communication was confirmed. The defect was approximately 1 cm in diameter and was situated within the fossa ovalis, with no evidence of tears extending beyond its rim.

Discussion

Individuals with some forms of congenital heart disease require an adequate interatrial communication for survival. The development of the Rashkind balloon septostomy procedure revolutionised the management of transposition of the great arteries in the neonatal period.[1] Other lesions, however, such as right or left atrioventricular valve atresia, frequently present after the neonatal period when balloon septostomy may be unsuccessful because of thickening of the atrial septum. Furthermore, even when balloon septostomy has been performed in the neonatal period, progressive restriction of the interatrial communication often develops.[3] For many years such patients have been palliated either surgically (with the Blalock-Hanlon atrial septectomy) or by Park's blade septostomy procedure in the cardiac catheterisation laboratory.[2] Both techniques sometimes do not achieve an adequate interatrial communication in the long term.[3] Furthermore, not all paediatric cardiologists are familiar with the technique of blade septostomy and it can be difficult or even hazardous to introduce a blade catheter into a small left atrium. Anaesthesia for surgical septectomy may also be quite hazardous in some extremely sick infants such as our second patient. The three cases presented show that balloon dilatation of the atrial septum may be an alternative technique for creating a large interatrial communication.

Experience with balloon dilatation of the atrial septum is limited,[4–7] and we do not know how its safety and efficacy compare with blade septostomy. In our youngest patient the dilatation procedure was initially highly successful in restoring cardiac output and adequate systemic saturations, but palliation was only sustained for two months. It is not known whether a procedure with larger balloons would have resulted in longer palliation. Certainly, the risks of the procedure, such as excessive tearing of the atrial septum beyond the fossa ovalis and damage to the femoral vessels, will be increased if large balloons are used in small infants. The only technical difficulty with the procedure that we have so far experienced was that of distal stripping of the atrial septum along the balloon in patient 3. If the procedure was performed solely under fluoroscopic guidance this stripping might go unnoticed because the position of the balloon might appear to be satisfactory. For this reason cross sectional echocardiographic monitoring should be an integral part of this procedure.

Experimental studies in animals showed that stationary balloon dilatation of the atrial septum produced atrial septal defects within the fossa ovalis without causing tears that extended into the adjacent atrial septum.[4] In 1987 a successful balloon dilatation procedure of the atrial septum was reported in an infant with transposition of the great arteries.[5] Recently a young adult with primary pulmonary hypertension was palliated by a similar procedure with a 12 mm × 40 mm balloon catheter after transseptal puncture with a Brockenbrough needle.[6] Finally, the recent follow up report of the Valvuloplasty and Angioplasty of Congenital Anomalies Registry outlined the results of a number of miscellaneous interventional catheterisation procedures from several centres.[7] In this review balloon atrial septal dilatation was reported in three infants with hypoplastic left heart syndrome. All three procedures were successful in the short term. One patient had "massive internal bleeding"; no specific details were given.

We showed that balloon dilatation enlarged the atrial septal defect in three children with differing congenital cardiac defects. Further reports of clinical experience are needed to establish the role of this procedure in relation to blade septostomy and surgical septectomy.

1 Neches WH, Mullins CE, McNamara DG The infant with transposition of the great arteries. II Results of balloon atrial septostomy. *Am Heart J* 1972,84:603–9.

2 Park SC, Neches WH, Mullins CE, *et al.* Blade atrial septostomy: collaborative study *Circulation* 1982,66. 258–66.

3 Perry SB, Lang P, Keane JF, Jonas RA, Sanders SP, Lock JE Creation and maintenance of an adequate interatrial communication in left atrioventricular valve atresia or stenosis. *Am J Cardiol* 1986;58:622–6

4 Mitchell SE, Kan JS, Anderson JH, White RI Jr, Swindle MM. Atrial septostomy: stationary angioplasty balloon technique [Abstract]. *Pediatr Res* 1986,20·173A.

5 Shrivastava S, Radhakrishnan S, Dev V, Singh LS, Rajani M. Balloon dilatation of atrial septum in complete transposition of great artery—a new technique. *Indian Heart J* 1987;39·298–300

6 Hausknecht MJ, Sims RE, Nihill MR, Cashion WR. Successful palliation of primary pulmonary hypertension by atrial septostomy. *Am J Cardiol* 1990,65 1045–6

7 Mullins CE, Latson LA, Neches WH, Colvin EV, Kan J Balloon dilation of miscellaneous lesions: results of Valvuloplasty and Angioplasty of Congenital Anomalies Registry *Am J Cardiol* 1990;65·802–3

Addendum

Since this paper was accepted three further procedures have been successfully performed: two in infants and one in a 17 year old boy with severe primary pulmonary hypertension.

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Successful intracardiac electrical conversion of atrial flutter in patients with complex congenital heart disease

David Cunningham, Jane Somerville, John A Kennedy, Edward Rowland, Anthony F Rickards

Abstract

Sixteen patients presenting on 21 occasions with atrial flutter in association with complex congenital heart disease were treated by intracardiac stimulation techniques combined with activation mapping. Nineteen episodes of atrial flutter were successfully converted to sinus rhythm. In the remaining two episodes atrial fibrillation was induced with spontaneous conversion to sinus rhythm within 12 hours in one episode and immediate DC cardioversion to sinus rhythm in the other. Intracardiac stimulation techniques were highly successful in this group and allowed reliable conversion to sinus rhythm without general anaesthesia and high energy cardioversion. In patients with atrial flutter associated with congenital heart disease intracardiac stimulation techniques should be tried first.

Atrial flutter is common after surgical repair of complex congenital cardiac malformations and it can have profound haemodynamic consequences, particularly when ventricular function is impaired. Both drug treatment and external cardioversion with high energy DC shock have disadvantages.[1–3]

Pharmacological agents can either allow the ventricular response to be controlled or may achieve chemical conversion to sinus rhythm. The conversion rate is low in these patients with congenital heart disease and residual lesions, especially when flutter has been present for a long time.

Even when the ventricular rate is controlled the circulation still lacks the atrial contribution to cardiac output and this may predispose the patients to worsening of atrioventricular valve regurgitation, particularly in hearts with one functioning ventricle, deteriorating right ventricular function in transposition of the great arteries, or in tetralogy of Fallot with pulmonary regurgitation. In general, the symptoms get worse when atrial flutter becomes established.

External DC cardioversion is effective in restoring sinus rhythm but it requires a general anaesthetic and the ventricular myocardium is liable to be damaged if repeated cardioversions are necessary. So it may be better to avoid cardioversion in a young patient with an abnormal ventricle. An alternative approach is to use intracardiac stimulation techniques to restore sinus rhythm Rapid overdrive pacing[4–7] and long duration single pulses ("atrioversion")[8] have both been successful.

We examined the results of these techniques in a group of young patients presenting with atrial flutter in association with a complex congenital cardiac malformation and deteriorating clinical state.

Patients and methods

METHODS

Patients were brought to the electrophysiological laboratory unsedated and in the post-absorptive state. Routine premedication for electrophysiological studies was used. The patients were routinely anticoagulated at the time of study. In most the study was performed as an elective procedure after the patient had been anticoagulated with oral anticoagulants for 4–6 weeks. In these patients warfarin was stopped for 24 hours before the study or until the International Normalised Ratio fell below 2. In those in whom the study was performed as an urgent procedure half dose heparinisation was used at the start of the catheterisation.

Under local anaesthesia we introduced one or more quadripolar electrode catheters (with 5 or 10 mm interelectrode spacing) from a femoral or subclavian vein and advanced the catheter(s) to the right atrium. In three episodes the catheter entered the left atrium because of an atrial septal defect or absent interatrial septum.

A surface electrocardiogram and intracardiac electrograms were recorded on a multichannel inkjet recorder. Endocardial stimulation was performed by manipulating the catheter(s) into various atrial sites. Four surface electrocardiographic leads were simultaneously recorded. Atrial sites were classified as high, mid, or low and as anterior, lateral, posterior, or septal in the right atrium. Left atrial stimulation was not performed.

Through one pair of electrodes we delivered stimuli with a pulse width of 2 ms at twice diastolic threshold. Single stimuli were introduced after variable programmed delays from the previous spontaneous flutter electrogram to scan the atrial flutter cycle. The initial delay was 10 ms less than the flutter cycle length; this was reduced until refractoriness was encountered. The duration of the post-stimulation (return) flutter cycle was noted. A non-compensatory return cycle resulted in the flutter being reset (type I response (fig 1)). A

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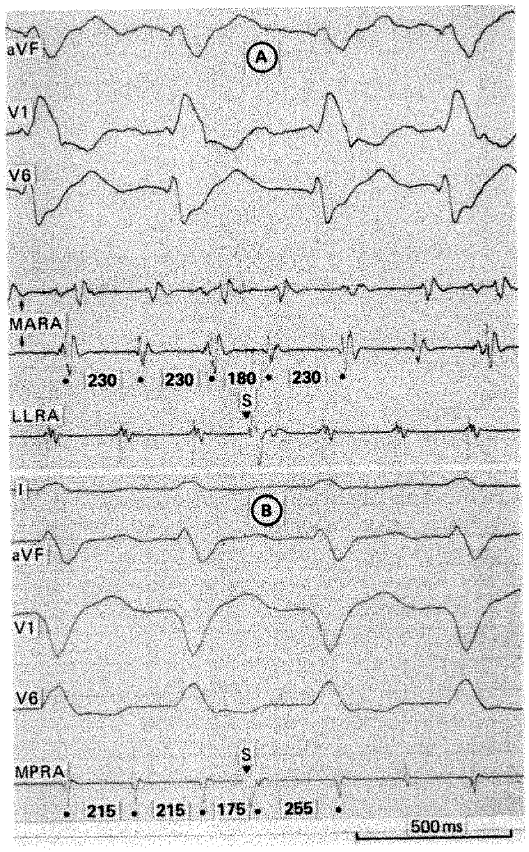

Figure 1 An example of reset (type I) and compensatory (type II) responses to atrial stimulation during flutter. (A) Three surface and three intracardiac leads (two from mid-anterior right atrium (MARA) and low lateral right atrium (LLRA)). Flutter cycle length is 230 ms. A premature stimulus at the low lateral site produced a cycle of 180 ms, followed by a non-compensatory return cycle of 230 ms (a type I response). (B) Four surface leads and one intracardiac lead from mid-posterior right atrium (MPRA). Flutter cycle length was 215 ms. A premature stimulus resulted in a cycle of 175 ms followed by a compensatory return cycle of 255 ms (175 + 255 = 2 × 215) (a type II response).

compensatory pause in the return cycle did not result in resetting (type II response). Further programmed stimuli (up to a total of four) were added if a type I response was found. Each additional stimulus was initially added at a coupling time 10 ms less than the flutter cycle length and reduced until refractoriness was encountered or conversion achieved.

If conversion was not achieved rapid atrial overdrive pacing was attempted with a modification of the protocol suggested by Waldo *et al.*[7] Pacing was begun 10 beats per minute faster than the flutter rate, initially for two seconds then if necessary for a further burst duration of four, eight, 15, or 30 seconds. If flutter persisted, the pacing rate was increased by 10 beats per minute and the sequence of burst durations was repeated. It is known that pacing rates that exceed 135% of the flutter rate are more likely to result in atrial fibrillation,[8] and these rates were not exceeded unless pacing had failed at lower rates at more than one site.

If conversion was not achieved a further type I atrial site was sought and the full stimulation protocol was repeated. If a suitable type I site could not be found the full conversion protocol was carried out at a type II site.

In one patient (two episodes) a new technique (Atrioversion[8]) was used instead of rapid atrial pacing, as part of an experimental protocol. A single constant current pulse with a duration 20 ms longer than the flutter cycle length was delivered 10 ms after the refractory period (as defined by a single stimulus) with an amplitude that was initially twice the diastolic threshold and was doubled to a maximum of 20 mA.

ELECTROCARDIOGRAPHIC DEFINITION OF ATRIAL FLUTTER

The diagnosis of atrial flutter was made from the surface electrocardiogram. The diagnosis required the presence of regular, rapid atrial activity with some degree of atrioventricular block, either spontaneously or during carotid sinus massage. An atrial rate of >200 beats per minute was required with clear evidence of classic flutter waves in at least one surface electrocardiographic lead. This rate is lower than the generally accepted lower rate limit for atrial flutter (240–250 beats per minute) because previous cardiac surgery and congenital abnormalities of the atrium can slow the flutter rate.

In episodes in which the atrial rate was below 200 beats per minute flutter was diagnosed only if the patient was receiving antiarrhythmic drug treatment likely to slow the atrial rate and if an earlier electrocardiogram had showed flutter at a rate greater than 200 with an identical flutter wave configuration before drug treatment.

Atrial flutter was classified as being of the "common" form if negative sawtooth deflections were seen in the inferior surface electrocardiogram leads and uncommon if the flutter waves were positive in leads I and II.

PATIENTS

Twenty one procedures were carried out on 16 patients (eight male, and eight female, aged 15–43 years, mean 26). Table 1 shows the clinical details. All patients had had previous corrective surgery for their congenital lesions on at least one and up to four occasions. Eleven patients had one procedure and five had two on separate hospital admissions. The duration of flutter before attempted conversion ranged from six hours to five years (median 14 days). At the time of study, the atrial rate was 158–363 beats per minute (mean 229) and the ventricular rate was 63–172 beats per minute (mean 100). 2:1 atrioventricular block was present in seven episodes, 3:1 block in four episodes, 1:1 conduction in one episode, and a variable block in the remainder.

The current antiarrhythmic drug treatment was amiodarone in seven episodes, digoxin in two episodes, digoxin and quinidine in two episodes, digoxin and disopyramide in two episodes, quinidine in one episode, amiodarone and digoxin in one episode, digoxin and flecainide in one episode, and xamoterol in one episode. In four episodes the patient was receiving no antiarrhythmic drug treatment at the time of study.

In five episodes the atrial rate was below 200 beats per minute. In four of these the patient was receiving amiodarone and had previous evidence of atrial flutter with an atrial rate of over 240 beats per minute before amiodarone and an identical flutter wave configuration. In the remaining episode, the flutter rate was 188 when the patient was receiving disopyramide and it accelerated to 330 in a subsequent episode when the patient's treatment was changed to xamoterol.

Conversion of atrial flutter was attempted only during episodes in which there was

Table 1 Data on patients

Case	*Age*	*Sex*	*Basic diagnosis*	*Previous surgery*	*Residual lesions*	*Previous arrhythmias*	*Previous treatment*	*Result of conversion and follow up*
1	17	M	VSD, infundibular pulmonary stenosis	VSD closure and resection of pulmonary stenosis (age 14)	Very small VSD, mild pulmonary stenosis	AFl + syncope (age 17) (requiring cardioversion)	Quinidine then amiodarone	Sinus rhythm, flutter recurred age 20, repeat conversion to sinus rhythm
2	33	F	ASD (ostium secundum)	ASD repair (age 33)		SVT + cerebral embolism (age 32)	Nil	Sinus rhythm
3	20	F	ASD (ostium secundum)	ASD repair (age 5)		Persistent atrial flutter since age 5	Digoxin + amiodarone	Sinus rhythm—reverted to atrial flutter 1 month; controlled by digoxin
4	28	M	Tetralogy of Fallot	L Blalock total repair (age 9)	Small VSD, pulmonary regurgitation, pulmonary stenosis, cardiomegaly	Atrial tachycardia (age 26), atrial flutter (age 28)	Amiodarone, digoxin, disopyramide	Sinus rhythm, flutter recurred age 31, repeat conversion to SR
5	31	M	VSD, infundibular stenosis, pulmonary hypertension	VSD closure infundibular resection (age 11)	Pulmonary hypertension, right heart failure	Atrial flutter (age 31)	Digoxin	Sinus rhythm, heart/lung transplant age 32
6	31	F	Tricuspid atresia, ASD	Pott's operation (age 18 months)	Tricuspid atresia, ASD	Atrial fibrillation (age 27), complete heart block (age 30) (pacemaker insertion)	Amiodarone, digoxin	Sinus rhythm
7	34	M	Tetralogy of Fallot, ASD, anomalous origin of LAD	Pott's operation (age 3) and total repair + ASD closure (age 14)	Pulmonary regurgitation, pulmonary stenosis, PA stenosis, anomalous origin LAD	Syncope age 30, ventricular extrasystoles	Digoxin	Sinus rhythm, flutter recurred age 35, repeat conversion to sinus rhythm
8	22	F	Tricuspid atresia, ASD, Fontan at age 12	Glenn's operation (age 8 months), L Blalock (age 8), Fontan (age 12), redo Fontan (age 22)		VT (age 19), ?SVT/VT (age 20)	Disopyramide, amiodarone	Sinus rhythm, flutter recurred age 23, repeat conversion to sinus rhythm
9	22	F	TGA, VSD, pulmonary hypertension	Blalock-Hanlon (age 2 months), banding of PA (age 18 months), palliative Mustard (age 8)	Pulmonary hypertension, VSD, tricuspid regurgitation	SVT (age 17)	Amiodarone	Sinus rhythm
10	15	M	Mitral atresia, doublet outlet LV, ASD	Blalock-Hanlon			Amiodarone	Sinus rhythm
11	19	F	PDA, ostium primum ASD, coarctation	PDA ligated (age 10 months), ASD repaired (age 5)	Coarctation of aorta	AVNRT/SN disease (age 11), antitachycardia pacemaker removed age 17 (infection)	Digoxin	Atrial fibrillation, immediately converted to sinus with 75 J DC
12	25	M	Tricuspid atresia	Fontan shunt			Amiodarone	Sinus rhythm
13	31	M	Univentricular heart, tricuspid atresia	Fontan (age 20), closure VA leak (age 28)	Calcified RA clot	Recurrent AFl since 2nd op	Quinidine, digoxin, disopyramide	Sinus bradycardia treated with xamoterol. AFl recurred after 2 months—repeat conversion to sinus rhythm
14	24	M	Tetralogy of Fallot	Total repair (age 8)	Pulmonary regurg, pulm stenosis	Recurrent AFl since age 18	Amiodarone	Sinus rhythm
15	43	F	Pulmonary stenosis	Pulmonary valvotomy (age 7) open pulmonary valvotomy + PFO closure (age 16)	Infundibular hypertrophy	Recurrent AFl since age 41	Digoxin, flecainide, verapamil	Sinus rhythm
16	33	F	ASD	ASD repair	Pulmonary stenosis		Digoxin	Sinus rhythm

AFl, atrial flutter; ASD, atrial septal defect; AVNRT, atrioventricular nodal reentrant tachycardia; LAD, left anterior descending coronary artery, LV, left ventricle, PA, pulmonary artery; PDA, patent ductus arteriosus, PFO, patent foramen ovale, RA, right atrium; SN, sinus node; SR, sinus rhythm, SVT, supraventricular tachycardia; TGA, transposition of great arteries; VA, ventriculoatrial; VSD, ventricular septal defect; VT, ventricular tachycardia.

evidence of regular atrial flutter on the surface electrocardiogram. Irregular atrial activity or atrial fibrillation was excluded. In 16 episodes, flutter was of the "common" form. In five episodes, flutter was classed as "uncommon".

Results

Table 2 shows the data gathered at electrophysiological study. All stimulation sites were in the right atrium. There was a type I response to atrial stimulation site in 16 episodes (81%) at 24 atrial sites. No response to attempted conversion was found at eight sites (mid-lateral 1, low lateral 1, high anterior 2, mid-anterior 2, mid-septal 1, mid-posterior, 1). The distribution of the 16 type I sites at which conversion occurred was: high lateral 3, mid lateral 2, low lateral 2, high anterior 2, mid-anterior 3, low anterior 1, mid-septal 1, high posterior 1, mid-posterior 1. In addition, three type II sites were found in these 17 episodes (mid-septal 1, low septal 1, high anterior 1). Conversion was not attempted at these latter sites.

Only type II responses were found at nine sites in five episodes. Conversion did not occur at four sites (mid-lateral 1, high anterior 1,

Table 2 Electrophysiological data on individual episodes

Case	*Age*	*Sex*	*Current treatment*	*Duration of flutter*	*Flutter type*	*Atrial rate*	*Ventricular rate*	*Stimulation site in RA*
1	17	M	Quinidine	2 days	Common	304	152	Mid-lateral
2	18	M	Amiodarone	1 day	Common	221	110	Mid-lateral
3	33	F	Nil	3 wk	Common	271	135	High lateral
4	20	F	Nil	5 yr	Common	218	109	Low lateral
5	15	M	Amiodarone	8 h	Uncommon	181	80	High anterior
6	31	F	Digoxin + quinidine	2 mnth	Uncommon	363	110	Low lateral
7	22	F	Nil	Unknown	Uncommon	206	103	Mid lateral
8	34	M	Nil	3 mnth	Common	252	126	Low septal
9	22	F	Digoxin + amiodarone	Unknown	Common	166	83	Low posterior
10	28	M	Amiodarone	18 mnth	Common	219	109	Mid posterior
11	31	M	Amiodarone	4 days	Common	176	88	High posterior
12	22	F	Amiodarone	2 days	Common	300	150	Low lateral
13	31	M	Digoxin + quinidine	2 wk	Common	206	75	High lateral
14	25	M	Amiodarone	Unknown	Common	172	172	High anterior
15	34	M	Digoxin + disopyramide	7 days	Common	237	79	Mid-anterior
16	31	M	Digoxin + disopyramide	7 days	Common	188	63	Mid-anterior
17	19	F	Digoxin	45 days	Uncommon	263	98	High anterior
18	31	M	Xamoterol	14 days	Common	330	110	Mid-anterior
19	24	M	Amiodarone	3 mnth	Common	158	79	High anterior
20	43	F	Digoxin + flecainide	4 mnth	Common	233	82	Low anterior
21	33	F	Digoxin	6 mnth	Uncommon	256	128	High lateral

mid-anterior 1, high septal 1). Conversion occurred at the remaining five sites (mid-lateral 1, low lateral 1, high anterior 2, low posterior 1).

Single atrial stimuli did not convert any episode of flutter. Conversion to sinus rhythm was achieved with programmed stimuli in six episodes. Figure 2 shows an example of conversion with two stimuli. Rapid atrial pacing resulted in conversion to sinus rhythm in 11 episodes (figure 3 shows one) and to atrial fibrillation in two. One of these latter two episodes had the most rapid atrial rate (363 beats per minute) and endocardial mapping showed coexisting areas of atrial fibrillation and flutter not suspected from the surface electrocardiogram; sinus rhythm spontaneously resumed 12 hours later. In the other episode where atrial fibrillation ensued, DC cardioversion was carried out immediately because the patient had documented sinus node disease and the atrial catheter would have allowed backup atrial pacing if required.

The remaining two episodes in one patient were converted to sinus rhythm by a single long constant current pulse ("atrioversion"[8]). Fifteen of the 19 conversions to sinus rhythm were at type I atrial sites.

One conversion to sinus rhythm after rapid atrial pacing was followed by profound, sustained sinus bradycardia, requiring atrial support pacing and subsequently isoprenaline infusion to maintain an adequate rate. The patient was subsequently treated with oral xamoterol, but had a further recurrence of atrial flutter two months later and was again successfully converted to sinus rhythm. Xamoterol was stopped and an atrial demand pacemaker was implanted.

Overall, 19 episodes (90%) were returned directly to sinus rhythm during the procedure. One patient, who had coexisting areas of atrial fibrillation not suspected from the surface electrocardiogram and was converted to atrial fibrillation, subsequently reverted to sinus rhythm after 12 hours. Clinical success was thus achieved in 20 episodes (95%). In all patients the clinical state improved.

Discussion

In patients with one functioning ventricle, as in tricuspid atresia or double inlet ventricle, the onset of atrial flutter causes a considerable symptomatic deterioration. Atrial flutter is also dangerous in other complex lesions, such as

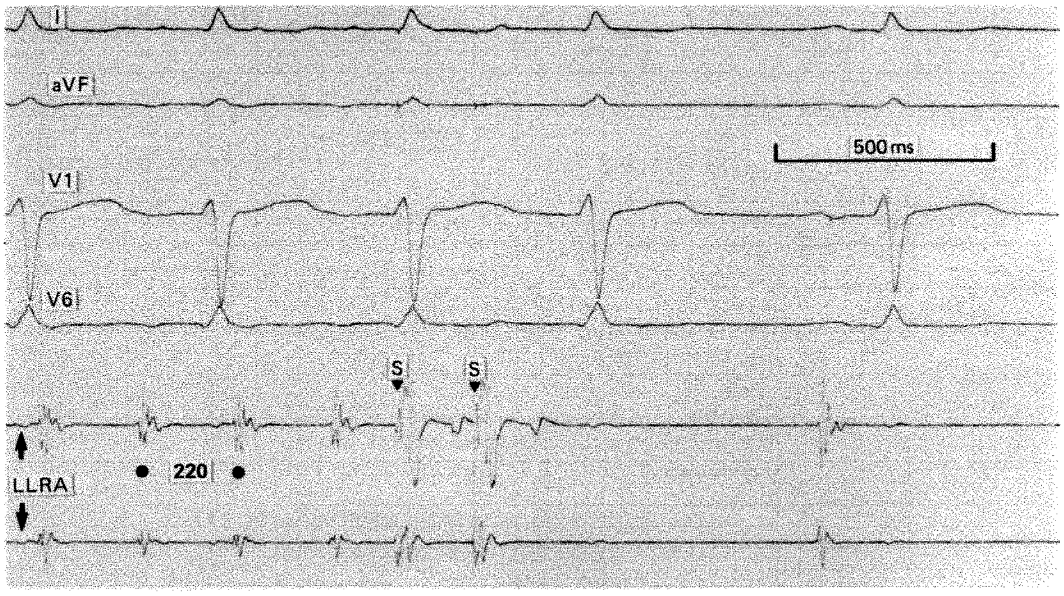

Figure 2 Conversion of atrial flutter to sinus rhythm by two premature atrial stimuli. Four surface electrocardiographic leads and two intracardiac electrograms showing atrial flutter with a cycle length of 220 ms. Two extrastimuli (coupling times 140 ms and 180 ms) caused immediate reversion to sinus rhythm.

Response type	*Conversion method*	*Result of conversion*	*Details of conversion*
Type I (reset)	Atrioversion	Sinus rhythm	
Type I (reset)	Atrioversion	Sinus rhythm	
Type I (reset)	Extrastimuli	Sinus rhythm	180/170 ms
Type I (reset)	Extrastimuli	Sinus rhythm	170/140 ms
Type II (non-reset)	Rapid atrial pacing	Sinus rhythm	CL 165 ms for 4 s
Type II (non-reset)	Rapid atrial pacing	Atrial fibrillation	CL 100 ms for 8 s
Type II (non-reset)	Extrastimuli	Sinus rhythm	270/250 ms
Type I (reset)	Extrastimuli	Sinus rhythm	155/140/140/140 ms
Type I (reset)	Extrastimuli	Sinus rhythm	270/210 ms
Type I (reset)	Rapid atrial pacing	Sinus rhythm	CL 200 ms for 4 s
Type I (reset)	Extrastimuli	Sinus rhythm	240/240/290 ms
Type I (reset)	Rapid atrial pacing	Sinus rhythm	CL 210 ms for 8 s
Type I (reset)	Rapid atrial pacing	Sinus rhythm	CL 200 ms for 4 s
Type II (non-reset)	Rapid atrial pacing	Sinus rhythm	CL 290 ms for 8 s
Type I (reset)	Rapid atrial pacing	Sinus rhythm	CL 160 ms for 4 s
Type I (reset)	Rapid atrial pacing	Sinus rhythm	CL 230 ms for 30 s
Type I (reset)	Rapid atrial pacing	Atrial fibrillation	CL 160 ms for 4 s
Type I (reset)	Rapid atrial pacing	Sinus rhythm	CL 150 ms for 8 s
Type I (reset)	Rapid atrial pacing	Sinus rhythm	CL 300 ms for 2 s
Type I (reset)	Rapid atrial pacing	Sinus rhythm	CL 170 ms for 4 s
Type I (reset)	Rapid atrial pacing	Sinus rhythm	CL 180 ms for 2 s

CL, cycle length.

tetralogy of Fallot. It is common in the third and fourth decades in both operated and unoperated patients with various defects of the atrial septum and anomalies of pulmonary venous drainage. As in all symptomatic arrhythmias two strategies are required. The first is prevention, which includes exclusion of a predisposing structural lesion, such as obstruction in a conduit connection used in the Fontan or right ventricular outflow reconstruction procedures. The second is restoration of sinus rhythm during the acute paroxysm. The major disadvantages of external DC cardioversion are that general anaesthesia is needed and that the myocardium of an already abnormal ventricle may be damaged. The attractions of endocardial conversion are obvious. The technique, however, requires that there is good venous access and that the atrial arrhythmia is regular. It cannot be applied to atrial fibrillation. In one of the two episodes in the present series where atrial fibrillation resulted from conversion, endocardial atrial mapping showed distinct coexisting areas of flutter and fibrillation that were not evident on the surface electrocardiogram. Conversion to sinus rhythm was thus unlikely in this episode.

For this study we selected patients with regular and rapid atrial arrhythmia. Patients with anomalies of systemic venous drainage were excluded owing to difficulties of access. Otherwise, it is our policy to start anticoagulation with heparin and to proceed to electrical conversion as soon as is possible. Appropriate antiarrhythmic medication to prevent recurrences is instituted or continued after conversion. We advise patients to return immediately if a further paroxysm occurs.

In the five instances in which the atrial rate was below 200 beats per minute during flutter, concomitant drug treatment accounted for the relatively slow atrial rate. A gradual lengthening of the flutter cycle without a change in flutter wave configuration was seen on sequential electrocardiographic recordings after treatment was started. Because this effect was consistent with the electrophysiological effect of amiodarone and disopyramide we thought that the mechanism of these slower rhythms must be identical and that they should remain classified as atrial flutter.

As well as having a high success rate, endocardial paced conversion of atrial flutter allows immediate atrial support pacing when there is sinus arrest after conversion—a facility not available during external cardioversion. This proved essential in one episode where profound sinus bradycardia followed conversion.

All of the study group had had previous corrective surgery, usually at an early age. None had a history of atrial arrhythmias before operation, and it is probable that the surgery contributed in a major way to creation of the substrate for their atrial flutter.

The procedure was highly successful in this group of patients. The mean procedure time

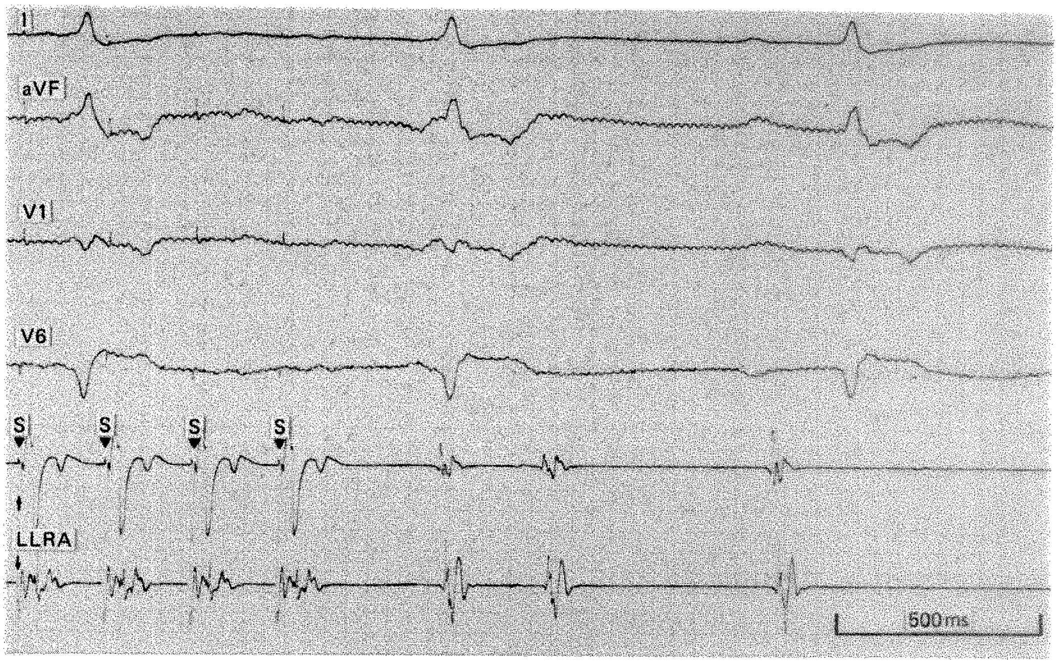

Figure 3 Conversion of atrial flutter to sinus rhythm by rapid atrial overdrive pacing. Four surface electrocardiographic leads and two intracardiac electrograms from the low lateral right atrium (LLRA) show the last four beats of an 8 s overdrive pacing train (cycle length 210 ms). After the end of pacing there were two atrial depolarisations, the first of which may be sinus in origin, followed by clear resumption of sinus rhythm.

was an hour, and theoretically the procedure could be carried out at the bedside under echocardiographic control. We believe that intracardiac electrical conversion is the best treatment for atrial flutter in patients with congenital heart disease because it avoids general anaesthesia and external cardioversion.

1 Dahl CF, Ewy GA, Warner ED, Thomas ED. Myocardial necrosis from direct current discharge. Effect of paddle electrode size and time interval between discharges. *Circulation* 1974;50:956–61.
2 Davis JS, Lie JT, Bentinck DC, Titus JL, Tacker WA, Geddes LA. Cardiac damage due to electrical current and energy Proceedings of the cardiac defibrillation conference, West Lafayette, Indiana Purdue University, 1975:27–32
3 Wilson CM, Allen JD, Bridges JB, Adgey AAJ. Death and damage caused by multiple direct current shocks: studies in an animal model. *Eur Heart J* 1988,9.1257–65.
4 Haft JI, Kosowsky BD, Lau SH, Stein E, Damato AN. Termination of atrial flutter by rapid electrical pacing of the atrium *Am J Cardiol* 1967;20:239–44.
5 Das G, Anand MK, Ankineedu K, Chinnavaso T, Talmers FN, Weissler AM. Atrial pacing for cardioversion of atrial flutter in digitalized patients. *Am J Cardiol* 1978,41:308–12.
6 Camm J, Ward D, Spurrell R. Response of atrial flutter to overdrive atrial pacing and intravenous disopyramide phosphate, singly and in combination. *Br Heart J* 1980;44.240–7.
7 Waldo AL, MacLean WAH, Karp RB, Kouchokos NT, James TN Entrainment and interruption of atrial flutter with atrial pacing. studies in man following open heart surgery *Circulation* 1977,56:737–45.
8 Cunningham AD, Kennedy JA. Atrioversion-conversion of atrial flutter in man using a long constant current pulse [Abstract]. *Br Heart J* 1985,53·93.

Br Heart J 1991;**65**:355–6

Pericardial haemorrhage causing right atrial compression after cardiac surgery: role of transoesophageal echocardiography

I A Simpson, C Munsch, E E J Smith, D J Parker

Abstract

After cardiac surgery transoesophageal echocardiography showed a large thrombus compressing the right atrium in three hypotensive patients. No satisfactory images were obtained by transthoracic imaging, which is often difficult in ventilated patients after cardiac surgery. Transoesophageal echocardiography, however, provided rapid diagnostic information and permitted prompt surgical intervention.

In patients who become hypotensive after major cardiac surgery it is often not easy to make the differential diagnosis between left ventricular dysfunction, prosthetic valve dysfunction, sepsis, cardiac tamponade, and intrathoracic bleeding. Echocardiography can provide additional information about the contractile state of the left ventricle and the function of prosthetic valves but transthoracic imaging in a ventilated patient after cardiac surgery is difficult. Transoesophageal echocardiography provides rapid, real time high resolution imaging of the heart and surrounding structures that is valuable in the management of these patients.

We describe three patients in whom compression of the right atrium by localised haematoma formation presented as either an early or late postoperative complication of valve surgery and in whom transoesophageal echocardiography was of primary diagnostic importance.

Case reports

CASE 1

A 59 year old woman with rheumatic mitral valve disease underwent mitral valve replacement with a 29 mm monostrut Björk-Shiley valve. Twelve hours after operation she became hypotensive and oliguric with peripheral vasoconstriction. Arterial blood pressure was 75 mm Hg systolic, central venous pressure 10 mm Hg, and mean left atrial pressure measured via a left atrial line was 30 mm Hg. Clinically, valve function seemed normal and there was no significant drainage from the intrathoracic drains. No satisfactory images could be obtained by transthoracic echocardiography. Transoesophageal echocardiography showed a large clot that surrounded and compressed the right atrium and extended superiorly around the superior vena cava (fig 1). Colour Doppler flow mapping showed that the right atrial cavity was less than 1 cm in diameter. The right ventricle and the left heart were underfilled and the mitral valve prosthesis seemed to be functioning normally. At reoperation the transoesophageal echocardiographic findings were confirmed and direct left atrial puncture showed a left atrial pressure of 5 mm Hg. The large haematoma was removed and haemostasis secured. The patient subsequently made an uneventful postoperative recovery.

CASE 2

A 66 year old man who had had a Carpentier-Edwards aortic valve replacement for aortic regurgitation and dilatation of the ascending aorta 10 years previously had the prosthetic valve replaced by a number 12 Starr-Edwards valve. The operative procedure was uncomplicated and the patient had an uneventful postoperative course. He was discharged seven days after operation. He was readmitted three days later with a history of increasing shortness of breath, a heart rate of 120 beats/min, and a systolic blood pressure of 70–80 mm Hg. There were no clinical signs of valve dysfunction or chest infection. The electrocardiogram showed atrial fibrillation with a rapid ventricular response and the chest *x* ray showed some cardiomegaly but clear lung fields. Echocardiography showed a large haematoma surrounding and compressing the right atrium, like that in patient 1. At reoperation there was a large clot compressing the right atrium contained by a partially obliterated pericardium. The source of bleed-

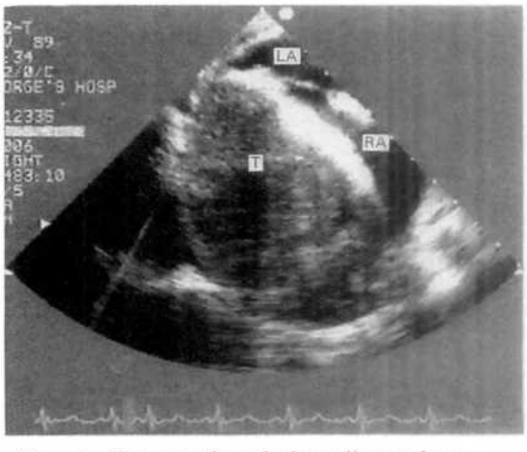

Figure 1 Transoesophageal echocardiogram from patient 1 showing a large round thrombus (T) compressing and almost completely obliterating the right atrial cavity (RA). LA, left atrium.

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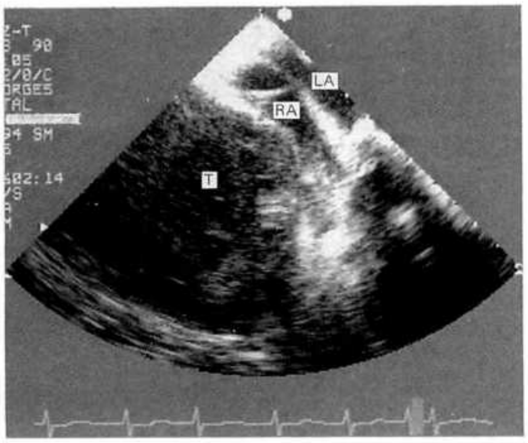

Figure 2 Transoesophageal echocardiogram from patient 3 showing a large area of thrombus (T) compressing the right atrial cavity. RA, right atrium, LA, left atrium.

ing was identified as an aortic tear posterior to the aortic suture line. The patient had a long postoperative course requiring prolonged ventilation but he remained haemodynamically stable and was discharged home. During subsequent outpatient follow up he has been symptomatically well though he has remained in atrial fibrillation with a controlled ventricular response.

CASE 3

A 69 year old woman underwent aortic and mitral valve replacement for severe mixed aortic and mitral valve disease with symptoms of increasing limiting exertional dyspnoea. The preoperative course was complicated by melena secondary to severe biventricular disease. The aortic and mitral valves were replaced with Carbomedics 23 mm and 31 mm valves. After slow mobilisation she was well enough to be discharged 12 days after operation but she was readmitted unwell two days later with hypotension and respiratory wheeze. Since discharge anticoagulation had become uncontrolled (International Normalised Ratio > 12). An initial diagnosis of chest infection was made but respiratory function deteriorated and she needed ventilation. Transoesophageal echocardiography (fig 2) showed a large haematoma surrounding and compressing the right atrium with mitral and aortic valves of normal appearance. At reoperation a very large clot was evacuated from the area surrounding the right atrium, the origin of bleeding at the aortic suture line was identified, and haemastasis was secured. Postoperatively the patient remained haemodynamically stable. No further haemodynamic problems developed but the patient eventually died of respiratory infection after prolonged ventilation.

Discussion

Transthoracic echocardiography after cardiac surgery is uniformly disappointing yet the information available from imaging the heart and surrounding structures is potentially very important in a critically ill patient. In the three patients we describe the pericardial haemorrhage would not have been recognised without transoesophageal echocardiography and appropriate surgical treatment would not have occurred. This experience is similar to that of Kochar *et al* who described localised pericardial haematomas in four patients causing right atrial compression after cardiac surgery.[1] These four patients had all undergone coronary artery bypass surgery whereas our patients developed localised haemorrhage after either mitral or aortic valve replacement.

Though haemodynamic information is valuable in patients after cardiac operations in patient 1 the findings of transoesophageal imaging—right atrial compression with an underfilled left heart—were at variance with the haemodynamic information. Hence, transoesophageal imaging allowed a valued clinical judgement of right atrial tamponade to be made and this led to prompt surgical evacuation of the haematoma; the diagnosis was not apparent with transthoracic imaging.

Transoesophageal echocardiography now allows high quality real time imaging of the heart and great vessels with a far greater spatial resolution than is possible with transthoracic imaging.[2] This is largely because of the superior signal/noise ratio and the ability to use higher frequency transducers than for transthoracic study without significantly limiting ultrasound attenuation. Transoesophageal imaging is already becoming accepted as a valuable technique for intraoperative diagnosis and guidance of surgery[3,4] but its role in the intensive care unit for diagnosis of postoperative complications is less well established. We describe three patients in whom transoesophageal echocardiography performed in the intensive care unit allowed a rapid diagnosis of a major complication of valve surgery which might not otherwise have been immediately evident. This somewhat unusual complication occurred in three patients over a period of only three months and may easily have been missed without transoesophageal imaging because the diagnosis may not be apparent from haemodynamic measurements. In particular, central venous pressure measurement may be misleading if the catheter tip does not lie at the site of compression. Chest x ray and conventional transthoracic echocardiography were unhelpful and more sophisticated imaging techniques such as computed tomography or magnetic resonance imaging would be impractical in these critically ill patients. Transoesophageal imaging is a valuable diagnostic tool in the intensive care unit, where the high resolution images obtained allow assessment of postoperative cardiac function, prosthetic valve function, and the presence of cardiac tamponade. We believe that this technique will become increasingly important in the management of patients after cardiac surgery.

1 Kochar GS, Jacobs LE, Kotler MN. Right atrial compression in postoperative cardiac patients: detection by transoesophageal echocardiography. *J Am Coll Cardiol* 1990;**16**:511–6.

2 Seward JB, Khandheria BK, Oh JK, *et al*. Transoesophageal echocardiography: technique, anatomical correlations, implementation and clinical applications. *Mayo Clin Proc* 1988;**63**:649–80.

3 Abel M, Nishimura R, Callagan M, Rehder K, Ilstrup D, Tajik A. Evaluation of intraoperative transesophageal two-dimensional echocardiography. *Anesthesiology* 1987;**66**:64–8.

4 Mitchell MM, Sutherland GR, Gussenhoven EJ, Taams MA, Roelandt JRTC. Transesophageal echocardiography. *J Am Soc Echo* 1988;**1**:362–77.

Br Heart J 1991;**65**:357–9

CASE REPORTS

Isovolumic relaxation sound: a new class of added heart sound?

C H Lee, D G Gibson

Abstract

An early diastolic sound in a patient with apical left ventricular disease is reported. Pulsed Doppler echocardiography showed blood flow within the left ventricular cavity during the isovolumic relaxation period whose peak flow velocity was synchronous with the onset of this diastolic sound. Because it occurred before filling started it could not have been either a third or fourth heart sound. It must thus represent a distinct and apparently unrecognised class of diastolic sound.

The third and fourth heart sounds have always been related to blood flow across the atrioventricular valves. When relaxation is asynchronous, however, blood flow can also occur within the ventricle during the isovolumic period. The associated changes in blood flow velocity may be rapid, raising the possibility that enough energy may be dissipated to generate a sound at a time when the atrioventricular valves are closed. We report such a case where flow during isovolumic relaxation period was associated with an added heart sound.

Case report

A 68 year old woman with aortic stenosis and three vessel coronary artery disease underwent aortic valve replacement and coronary bypass grafting. Postoperatively a left pleural, which had effusion developed and she remained unwell. Cardiomegaly was noted and diastolic added sounds were heard. It was believed that she might have suffered a perioperative infarction, which had impaired left ventricular function.

Two diastolic added sounds were confirmed by phonocardiography, one starting 90 ms and the other 190 ms after aortic closure (A_2) (fig 1A). Cross sectional echocardiography showed apical wall motion abnormality with moderate impairment of basal left ventricular function. Pulsed Doppler, recorded at the chordal level with the transducer at the apex, showed a summation mitral filling pattern: a single flow velocity pulse occurring in early diastole soon after the second heart sound but also after the P wave on the electrocardiogram. This pulse was preceded by striking flow away from the apex during isovolumic relaxation lasting 150 ms and reaching a peak velocity of 0·75 m/s. The timing of its peak velocity was synchronous with the onset of the first diastolic sound (X, fig 1B). That of the

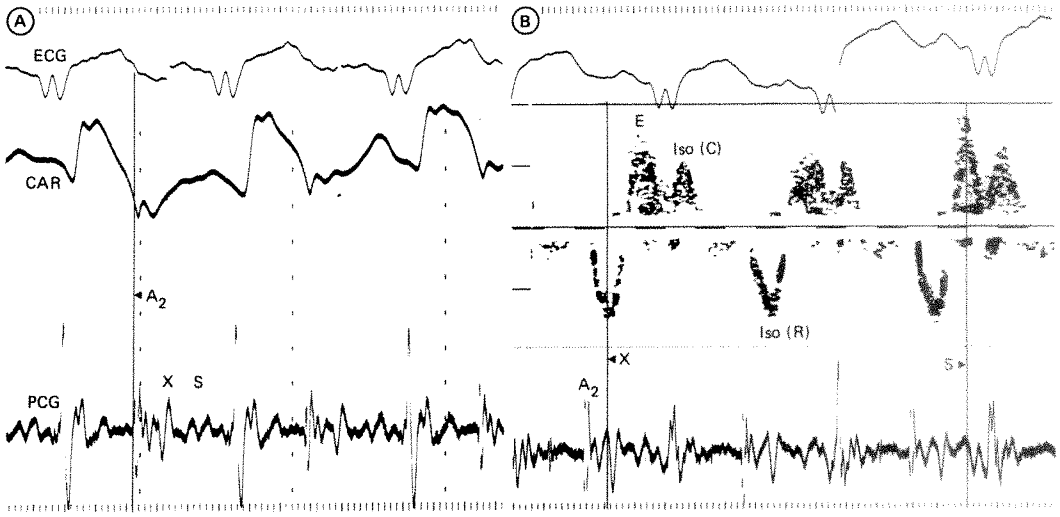

Figure 1 (A) Simultaneous recordings of electrocardiogram (ECG), indirect carotid pulse (CAR), and phonocardiogram (PCG). Aortic closure (A_2) corresponds to the dicrotic notch on the carotid pulse and is followed by two added diastolic sounds (X and S). (B) Pulsed Doppler recording at chordal level of the left ventricle for optimal registration of flow velocity during isovolumic relaxation period (Iso(R)). Early diastolic summation filling velocity (E) and flow during isovolumic contraction period (Iso(C)) are also shown. The onset of the first diastolic added sound (X) after aortic closure (A_2) corresponded in time to the peak isovolumic relaxation flow velocity and that of the second diastolic sound (S) to peak summation wave velocity. Full scale deflection ± 2 kHz. Time marker 20 ms.

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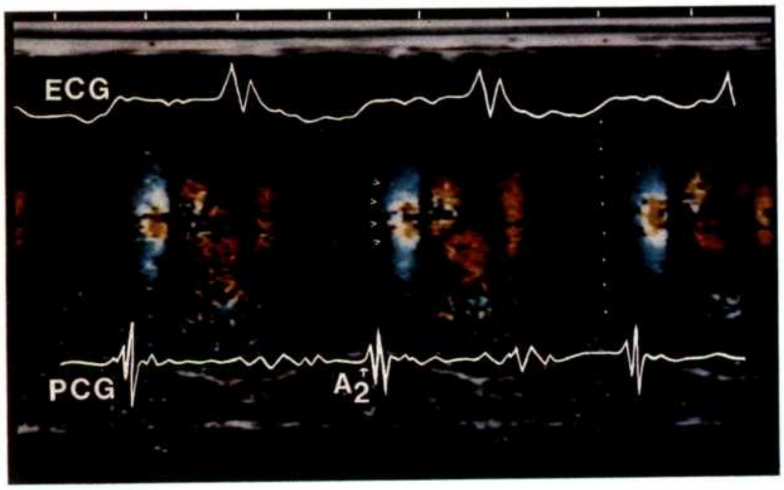

Figure 2 Colour M mode recorded from the apex, directed towards the mitral ring and left atrium, with simultaneous electrocardiogram (ECG) and phonocardiogram (PCG). Forward flow from left atrium to left ventricle is coded in red. Note the abnormal flow, coded blue (arrows), that immediately follows A_2 and precedes the onset of forward flow. This corresponds to blood flow from apex to base during isovolumic relaxation. For clarity of reproduction, the electrocardiogram and phonocardiogram have been retraced. Depth markers 1 cm, time marker 200 ms.

second diastolic sound (S, fig 1B), 100 ms later, coincided with peak early diastolic transmitral flow velocity. There was also an abnormal flow signal from base to apex after mitral closure during the isovolumic contraction period, but this was not associated with an additional heart sound (fig 1B). On the right side, peak early diastolic flow velocity across the tricuspid valve was synchronous with that across the mitral valve. Pulmonary valve closure, timed from pulmonary valve artefact, followed A_2, by 10 ms in expiration. The left ventricular flow disturbance was further examined by colour flow mapping. Abnormal flow was centred at the junction between normally moving and diseased segments of the left ventricle and was directed from the apex to the base. Colour M mode confirmed that this flow occurred during the isovolumic relaxation period, lasting for 150 ms and involving a column of blood 5 cm in length (fig 2).

Discussion

A diastolic heart sound is always an important clinical finding in a patient with heart disease. Though there is no consensus on how such sounds are generated, it is generally accepted that they are related in some way to ventricular filling—the third sound to filling in early diastole and the fourth to atrial systole. We, and others, have suggested more specifically that they represent energy dissipated by sudden changes in blood flow velocity.[1 2] On this basis, the third sound is synchronous with the transition from an accelerating to a decelerating flow during early diastole, and the fourth sound with the onset of acceleration caused by atrial systole. If this explanation is correct, one might expect diastolic sounds to be generated whenever there is a sudden change in blood flow velocity.

Blood flow within the left ventricle during isovolumic relaxation is a common finding and it has been documented in normal individuals as well as in patients with left ventricular hypertrophy.[3] Because blood is incompressible, this flow is the natural consequence of a change in left ventricular cavity shape during a period of constant ventricular volume. We have previously analysed such changes in detail as they occur in patients with coronary heart disease.[4] The change itself is caused by asynchronous relaxation, the onset of outward wall motion being characteristically delayed in segments of the myocardium supplied by diseased coronary arteries. These findings can be directly applied in the present case. The patient had apical disease, where the onsets of tension rise and fall are likely to have been delayed, and thus asynchronous with those at the base of the heart. Such differences in wall tension are the direct cause of the abnormal blood flow we observed, initially from base to apex during isovolumic contraction and reversing during isovolumic relaxation.

The onset of the added heart sound in this patient corresponded with the peak of the flow transient within the ventricle, when there was a sudden change from acceleration towards base to acceleration towards the apex. The added sound thus bore the same time relation to the changing blood flow as the classic third heart sound does to changing blood flow velocities during rapid filling.[1] It differed from a third heart sound in that it occurred before mitral valve opening, and so could not have been in any way related to rapid ventricular filling. In addition, the patient had a second added sound later in diastole whose onset corresponded with the peak right and left ventricular filling velocities. Because both mitral and tricuspid flow were summation waves this second diastolic sound was a summation rather than a fourth heart sound. Finally, aortic and pulmonary closure were effectively synchronous, which excludes delayed P_2 as a possible mechanism. We conclude, therefore, that in this patient the sudden reversal in the direction of blood flow within the ventricular cavity during isovolumic relaxation was the cause of the added sound in our patient.

Asynchronous relaxation and the resulting blood flow within the left ventricular cavity is common in normal hearts as well as in left ventricular hypertrophy and coronary artery disease. A possible associated heart sound, however, has received little attention. In part this may reflect the lamentable disuse into which the valuable art of phonocardiography has fallen. An additional cause is that the timing of the intraventricular blood flow was very abnormal in our patient because isovolumic relaxation itself was prolonged. It is much more common for peak isovolumic velocities to coincide with mitral or aortic valve closure, so that any vibrations they might generate are superimposed on the normal first or second, making a possible additional contribution difficult to document.

Our observation of a loud sound during isovolumic relaxation emphasises that it may be necessary to modify current nomenclature. Rather than calling any low pitched early diastolic sound a "third", we suggest the term should be applied only to vibrations occurring during the rapid filling phase of one or other ventricle and "fourth" to those associated with atrial systole. The sound we have described is not covered by either of these terms, and may be better called a "left ventricular isovolumic relaxation sound". Even this more complex term may prove unsatisfactory because the flow velocity associated with it was in the reverse direction to that more commonly seen during isovolumic relaxation.[3] Nevertheless, its association with a flow reversal within the ventricle provides further evidence that sudden changes in blood velocity are a general mechanism by which diastolic sounds can be produced.

It is thus clear that not all early diastolic sounds, even in patients with obvious left ventricular disease, are third heart sounds. This conclusion may be important when attempts are made to elucidate the pathological importance of such sounds. Third heart sounds should thus be clearly documented as such, particularly when their supposed presence is used to diagnose "heart failure" or made an indication for drug administration.[5] Finally, it is increasingly being recognised that disturbed diastolic function is clinically important in patients with heart disease; our observations show that interrelations between heart sounds and blood flow may provide useful information and may extend simple clinical approaches to this important area of cardiology.

1 Vancheri F, Gibson D. Relation of third and fourth heart sounds to blood velocity during left ventricular filling *Br Heart J* 1989;61 144–8

2 Pozzoli M, Febo O, Tramarin R, Pinna G, Cobelli F, Specchia G. Pulsed Doppler evaluation of left ventricular filling in subjects with pathologic and physiologic third heart sound. *Eur Heart J* 1990;11·500–8.

3 Sasson Z, Hatle L, Appleton CP, Jewitt M, Alderman EL, Popp RL Intracardiac flow during isovolumic relaxation: description and characterization by Doppler echocardiography. *J Am Coll Cardiol* 1987;10:539–46

4 Gibson DG, Prewitt TA, Brown DJ Analysis of left ventricular wall movement during isovolumic relaxation and its relation to coronary artery disease. *Br Heart J* 1976;38:1010–9.

5 Lee DCS, Johnson RA, Bingham JB, *et al*. Heart failure in outpatients. A randomised trial of digoxin versus placebo. *N Engl J Med* 1982;306:699–705.

Br Heart J 1991;65:360–2

Early constrictive pericarditis and anaemia after Dressler's syndrome and inferior wall myocardial infarction

Po Kee Cheung, Mary Lee Myers, J Malcolm O Arnold

Abstract

Early constrictive pericarditis and anaemia developed in a 52 year old man after he had an inferior wall myocardial infarction complicated by Dressler's syndrome. Total pericardiectomy at the time of coronary artery bypass surgery resulted in complete resolution of signs and symptoms.

Constrictive pericarditis after myocardial infarction has been rarely reported. There are three reports of this complication developing six to 12 months after frank haemopericardium had occurred with prophylactic anticoagulant treatment.[1-3] However, three recent cases occurred in the absence of an overt haemopericardium during the initial post-infarction period and two of these patients did not receive anticoagulants.[4 5] The third received an eight week course of anticoagulants for venous thrombosis but this was started four months after his presentation with myocardial infarction and pericarditis.[6] All six patients had evidence of clinical pericarditis during the acute myocardial infarction and in two patients Dressler's post-myocardial infarction syndrome preceded the development of constrictive pericarditis by six months and 10 months.[4 5] Anaemia developed in only one patient and the bone marrow aspirate was consistent with the diagnosis of anaemia of chronic disease. We describe a patient with an inferior wall myocardial infarction who developed constrictive pericarditis and reversible anaemia a month after Dressler's syndrome. Pericardiectomy corrected the constriction and the symptoms resolved.

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Case report

A 52 year old man was admitted because of acute onset (five hours before) of sharp left sided chest pain which was made worse by breathing and lying down but was improved by sitting forward. He was a long term smoker and had no history of angina or tuberculosis. Physical examination showed a triphasic pericardial rub and bi-basilar crackles but no paradoxical pulse or increase in jugular venous pressure. There were significant Q waves and flattened T waves in the inferior leads of the electrocardiogram with T wave inversion in I, aVL, and V4–V6. There was no ST elevation to suggest acute myocardial injury or pericarditis. Chest *x* ray showed mild cardiomegaly and pulmonary congestion and a small loculated pleural effusion. The echocardiogram showed inferoapical akinesis with hypokinesia of the septum and inferior wall. No pericardial effusion was detected. The clinical diagnosis was Dressler's syndrome complicating an inferior myocardial infarction, though it was not possible to determine clearly the timing of the infarction. No serial changes in the electrocardiogram or cardiac enzyme activities were seen. A viral aetiology was considered unlikely because the patient had no preceding history of a recent viral illness and his total and differential white cell counts on admission were normal.

He was treated with indomethacin 50 mg three times daily for three days then 25 mg three times daily for an additional three days. His pericardial rub and crackles resolved within 48 hours. Neither subcutaneous heparin nor oral warfarin were given. A treadmill exercise test (modified Bruce protocol) was carried out five days after admission and was abnormal with chest pain and ST segment elevation in the inferolateral leads. Cardiac catheterisation showed severe triple vessel coronary artery disease. The right coronary artery was totally occluded in its mid third as was the left anterior descending artery beyond the first major septal perforator. The circumflex artery seemed free of important disease but there was a 75% proximal stenosis of the intermediate artery. The left ventriculogram showed inferoapical akinesis and a left ventricular ejection fraction of 35%. He was accepted for coronary artery bypass surgery and discharged on once daily atenolol (100 mg) and enteric coated aspirin (325 mg).

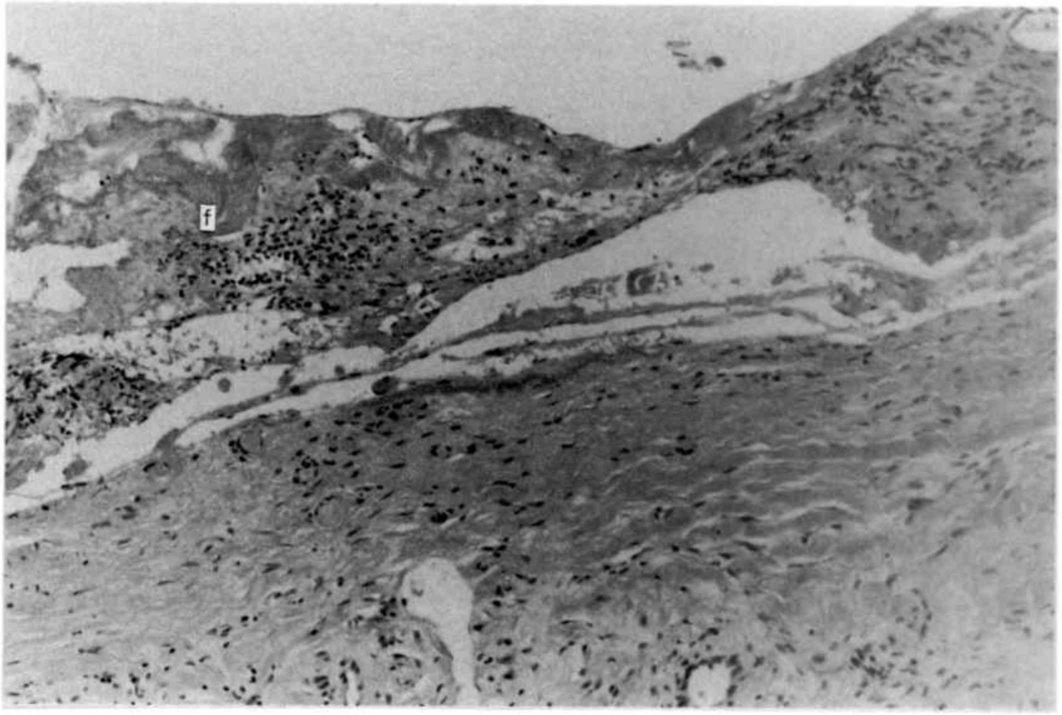
He remained free of symptoms for three weeks when he was readmitted because of increasing shortness of breath with anorexia, abdominal and chest discomfort, orthopnoea, and peripheral oedema. Physical examination showed an increased jugular venous pressure of 10 cm above the sternal angle, pulsus paradoxus (15 mm Hg difference), bi-basilar crackles, moderate peripheral oedema, and a mild degree of ascites but no pericardial friction rub. The electrocardiogram had not changed and there were no subsequent changes in serial activities of cardiac enzymes. Because of some clinical evidence suggestive of bi-ventricular failure, he was initially treated with diuretics and intravenous dobutamine and within 24 hours he responded well. An echocardiogram obtained after the start of this treatment showed moderate pericardial effusion and possible early diastolic collapse of the right ventricle. Repeat echocardiogram five days later showed resolution of the pericardial effusion and abnormal right ventricular motion. His haemoglobin had dropped from 139 g/l at the first admission to 116 g/l, without any evidence of blood loss or haemolysis. Red cell indices and white cell and platelet counts remained normal.

He was readmitted two weeks later because of increasing orthopnoea with more abdominal distension. Physical examination showed a much increased jugular venous pressure (12 cm above the sternal angle), no pulsus paradoxus, a tender liver enlarged to 3 cm below the right costal margin, moderate ascites, peripheral oedema, and bi-basilar crackles. Again, the electrocardiogram showed no new changes. The echocardiogram showed the previous segmental wall motion abnormalities, no pericardial effusion, but evidence of a paradoxical ventricular septal motion though without appreciable thickening of the pericardium. His haemoglobin concentration had dropped further to 103 g/l with normocytic normochromic indices. Reticulocyte count, serum B12, and folate and ferritin concentrations were normal. Antinuclear factor was negative. Bone marrow biopsy showed only non-specific reactive changes. He was treated with diuretics and his clinical state improved somewhat. The decision was made to proceed with surgery.

At operation the anterior pericardium was found to be grossly thickened and firmly adherent to the underlying right ventricle and adjacent portion of the left ventricle as well as to the proximal segments of the aorta and pulmonary artery. There was old haemorrhagic and fibrinous exudate over the anterior aspect of the right atrioventricular groove and right atrium. There was evidence of an earlier large inferior infarction. There was an extensive epicardial inflammatory reaction which made it difficult to identify the coronary vessels. The left internal thoracic artery was used to construct a bypass to the left anterior descending artery and a saphenous vein bypass graft was placed to the intermediate artery. Total pericardiectomy was performed and a significant improvement in right ventricular contractility was noted at the end of the procedure. The right atrial pressure decreased from 25 mm Hg before operation to 17 mm Hg after operation. By the second postoperative day, it had fallen to 14 mm Hg. Pathological examination of the excised pericardium showed chronic inflammatory infiltrate throughout its entire thickness (fig) with adherent thrombotic material. One month after operation, the jugular venous pressure was normal and the ascites, peripheral oedema, and hepatomegaly had resolved. A radionuclide blood pool ventriculogram showed normal right ventricular contractility with a right ventricular ejection fraction of 55%. The left ventricle showed inferior segmental wall motion abnormalities and an ejection fraction of 45%. His haemoglobin concentration returned to normal without further need for transfusion after operation. He remained well and symptom free eight months after surgery.

Discussion

The incidence of early pericarditis during myocardial infarction is reported to vary from 6% to 23%.[7] Dressler's post-myocardial infarction syndrome occurs in up to 4% of patients.[8] A single episode is usually self-limited and responds well to treatment with a non-steroidal anti-inflammatory agent as in this patient. The syndrome may recur though the long term sequelae are not clearly defined. It can be diffuse and may obliterate the pericardial sac, but subsequent development of constrictive



Thickened pericardium showing fibrin (f) and inflammation. (Original magnification × 25.)

pericarditis has been reported only twice and has occurred six to 10 months after the initial myocardial infarction.[4,5] In this patient constrictive pericarditis developed one month after Dressler's syndrome in the absence of prior anticoagulation and in association with anaemia. Some degree of intrapericardial haemorrhage was evident during surgery and histological examination also showed thrombotic material adherent to the pericardium. It is possible that severe pericarditis will cause leakage of blood into the pericardial sac though its contribution to the progression of constrictive pericarditis is not known. All three cases have occurred in men with an inferior wall myocardial infarction. Whether this is a chance association or relates to an anatomical factor, such as increased adherence of the inferior pericardium to the diaphragm or myocardium, is not known. All showed an excellent response to pericardiectomy.

A few cases of protracted Dressler's syndrome have been associated with anaemia, but the aetiology was not clear because bone marrow studies were not performed.[9] Our patient showed the development of early reversible anaemia and constrictive pericarditis in Dressler's syndrome similar to that reported by Kanawaty *et al.*[5] Bone marrow biopsy in both cases showed non-specific changes. It is possible that myocardial injury initiated an immune reaction leading to both pericarditis and anaemia. It is interesting to speculate that the early development of anaemia may be a marker for a more severe immune response. Recent evidence suggests that inflammatory mediators, such as interleukin 1, released in severe inflammatory conditions may decrease the erythroblast response to erythropoietin and cause anaemia which may respond to corticosteroids.[10] A recent retrospective analysis of a related condition, postpericardiotomy syndrome, concluded that steroids, non-steroidal anti-inflammatory drugs, or the combination did not seem to prevent the future development of constrictive pericarditis.[11] A prospective controlled trial in tuberculous pericarditis suggested that adjunctive treatment with prenisolone improves clinical symptoms and survival as well as reducing pericardiocentesis and possibly pericardiectomy.[12] Further studies may be needed to resolve this issue in the subgroup of patients with Dressler's syndrome and anaemia.

Dr J M O Arnold is the recipient of a Career Health Scientist Award from the Pharmaceutical Manufacturers Association of Canada. We thank Dr M Troster for the pathological analysis of the pericardium

1 Laszlo MH. Constrictive pericarditis as sequel to hemopericardium. report of a case following anticoagulant therapy. *Ann Intern Med* 1957,46 403–13

2 Beaufils PH, Bardet J, Temkine J, Masquet CH, Sebastien PH, Zelasko Y. Syndrome de Dressler: pericardite constrictive post-infarctus opérée avec succès. *Arch Mal Coeur* 1975,68.651–6.

3 Karim AH, Salomon J. Constrictive pericarditis after myocardial infarction: sequela of anticoagulant-induced hemopericardium *Am J Med* 1985;79.389–90

4 Goldhaber SZ, Lorell BH, Green LH. Constrictive pericarditis, a case requiring pericardiectomy following Dressler's post myocardial infarction syndrome. *J Thorac Cardiovasc Surg* 1981;81:793–6.

5 Kanawaty DS, Burggraf GW, Abdollah H. Constrictive pericarditis and anaemia post myocardial infarction. *Can J Cardiol* 1989;5(30) 147–8.

6 Ramsdale DR, Epstein EJ, Coulshed N Constrictive pericarditis after myocardial infarction. *Br Heart J* 1986; 56·476–8

7 Toole JC, Silverman ME Pericarditis of acute myocardial infarction. *Chest* 1975,67.647–53.

8 Davidson C, Oliver MD, Robertson RF. Post-myocardial infarction syndrome. *BMJ* 1961;ii·535–9.

9 Glasser M. Post-myocardial infarction syndrome with anaemia. *Conn Med J* 1970,34 413–4

10 Schooley JC, Kullgren B, Allison AC Inhibition by interleukin-I of the action of erythropoietin on erythroid precursors and its possible role in the pathogenesis of hypoplastic anaemia *Br J Haematol* 1987,67 11–5

11 Cimino JJ, Kogan AD Constrictive pericarditis after cardiac surgery report of three cases and review of the literature *Am Heart J* 1989;118·1292–301.

12 Strang JIG, Kakaza HH, Gibson DG, *et al.* Controlled trial of complete open surgical drainage and of prednisolone treatment of tuberculous pericardial effusion in Transkei *Lancet* 1988,ii 759–64.

BRITISH CARDIAC SOCIETY NEWSLETTER

The new offices of the society are now complete. We have recently taken over a fourth room, giving us all the top floor of numbers 1 and 2 St Andrew's Place. One of these will usually be available during office hours to any member in the neighbourhood and wishing for a quiet room in which to read, or simply to admire the superb view from the third floor over Regent's Park. Elaine Brown and Jennie Lodge would be happy to see members making use of this facility. They know the names of members of the society and many of the voices, but they complain that few faces are familiar to them. Please take the opportunity to visit the offices and to make yourselves known: you will be very welcome.

Members of the society have been inquiring about implementation of the new training programme, which comprises three years at registrar grade and three at senior registrar grade. Many have expressed a wish for their centres or district general hospitals to be included in the new registrar rotations and have completed forms for the Joint Committee on Higher Medical Training office. Up to the time of writing, the Royal College of Physicians of London and the Joint Planning Advisory Committee have not agreed on the number of registrar posts for medicine as a whole, and therefore the number protected for cardiology cannot be decided. We hope for early progress, but even after numbers have been decided much difficult work will have to be done by the college, the Specialty Advisory Committee, and perhaps by our own Training and Manpower Committee. We will keep you informed as best we can.

Can there be life after RITA? The question has been posed by John Hampton. With the RITA (Randomised Intervention Treatment of Angina) trial nearing the end of its recruitment phase, the steering committee decided at a meeting in the autumn to consider the possibility of the group undertaking further trials of intervention. After a brief discussion of the possibilities, the decision was made to hold a clinical trials workshop under the joint sponsorship of the British Cardiac Society and the British Heart Foundation. The meeting was organised by John Hampton and Stuart Pocock; it was held at the British Heart Foundation on 15 March. After introductory presentations as a background to clinical trials by Desmond Julian and Tom Ryan (on sabbatical leave from Boston), four trial protocols were presented. Raphael Balcon presented LIFT, a trial already in progress to examine the use of late intervention following myocardial infarction. Rob Henderson presented a proposal for a trial to compare PTCA and medical therapy in patients with angina who had had an angiogram, but who were found to have relatively mild disease so that either form of treatment would be technically possible and clinically reasonable. Man Fai Shui presented a protocol designed to investigate the use of angioplasty in patients with unstable angina. Bob Wilcox presented a trial designed for district general hospitals rather than cardiac centres, in which patients with stable angina whose symptoms could be adequately managed with medical therapy were randomly allocated to coronary angiography (and to defined intervention thereafter) or to a continuation of medical treatment. All four trial protocols were discussed in detail in an air of cheerful criticism . . . As a result, all the protocols were undoubtedly improved. All agreed that this had been a good forum, both to acquaint people interested in trials with the new proposals, and also to seek advice on the protocols from a group of physicians and surgeons with a wide range of backgrounds. Involvement in trials is relatively new to the British Cardiac Society. There are many forms that this may take: cooperation in the development of protocols for multicentre studies is particularly welcome and is one that we hope may be repeated. It may also be appropriate to help with modest funding through the new Medial Practice Committee, particularly for trials unlikely to attract support from the major funding bodies or from the pharmaceutical industry. Some pilot studies may be in this category.

More news of reports. The Fourth Joint Colleges Report on the Provision of Services for the Diagnosis and Treatment of Heart Disease will soon be ready for publication. The reports come out about every five years. The last was in 1985. They are influential because the support of the Royal College of Physicians of London and the Royal College of Surgeons of England is both powerful and not partisan as regards special pleading. Sadly, however, many of the recommendations of the last report have not been adequately implemented. The new report restates some important points that have been presented persuasively in the past. There is also a report soon to emerge from a joint working group from the Royal College of Physicians of London on cardiological intervention in elderly patients. The committee that compiled the report was chaired by Professor Maurice Lessof and the cardiac representatives were Desmond Sheridan, Michael Joy, and Ken Taylor. The important needs of the elderly for both medical and interventional treatment of cardiac disorders are often overlooked or disregarded. They tend to suffer disproportionately from rationing of scarce resources. But we should not overlook their needs. An increase in the average age of the population is an important demographic change that will continue over many years. Moreover, the elderly may benefit greatly from the technological aspects of modern cardiology that include pacing, surgery, and angioplasty. The report will be timely and welcome.

Our colleagues in the Société Française de Cardiologie are very active, and hold several meetings each year. In January they introduced their first "Journées Européennes". Your President represented the British Cardiac Society, but the support from the United Kingdom was sparse—perhaps because the event was not widely publicised here. That may be our fault, so let us make amends by suggesting that members consider attending the second meeting, which will take place in Paris from 16 to 18 January 1992. Abstracts have to be received by 15 July. More information can be obtained from SFC, 15 rue de Madrid, 75008 Paris. (Tel: 33 1 43 87 95 14). Knowledge of French is not essential—excellent simultaneous translation was available this year in the principal hall. It is a meeting that you would enjoy supporting

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NOTICES

1991

The **7th International Symposium on Cardiopulmonary Emergencies** will be held in Rotterdam on 19 to 22 November: Dr O Prakash, Thorax Centre, Dijkzigt Hospital, Dr Molewaterplein 50, 3015 GD Rotterdam, The Netherlands (Fax. 31 10 463 5240; Tel: 31 10 463 5230).

The **6th Congress of Western Pacific Association of Critical Care Medicine** will be held in Bangkok on 1 to 4 December· Secretariat Office, 6th WPACCM, Department of Anaesthesiology, Siriraj Hospital, Bangkok 10700, Thailand

The **8th Congress of "L'Information Cardiologique" on Advances in Cardiology** will be held in Paris on 6 and 7 December: Dr A Castillo-Fenoy, L'Information Cardiologique, Centre Cardiologique du Nord, 32–36 avenue des Moulins Gémeaux, 93200 Saint Denis, France (Fax: (1) 48 20 09 52; Tel· (1) 49 33 41 41 —(1) 48 20 18 21

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The **2èmes Journées Européennes de la Société Française de Cardiologie** will take place in Paris on 16 to 18 January (deadline for submission of abstracts is 15 July 1991): SFC, 15 rue de Madrid, 75008 Paris, France (Fax: (33) 1 43 87 17 14; Tel: (33) 1 43 87 95 14.

The Annual Meeting of the **British Cardiac Society** will take place at the Harrogate International Centre on 26 to 29 May.

The **13th International Symposium on Computer Assisted Decision Support and Database Management in Anaesthesia, Intensive Care and Cardiopulmonary Medicine** will be held in Rotterdam on 10 to 12 June: Dr O Prakash, Thorax Centre, Erasmus University, 3000 DR Rotterdam, The Netherlands (Fax: 31 10 463 5240; Tel: 31 10 463 5230).

Br Heart J 1991;65:364

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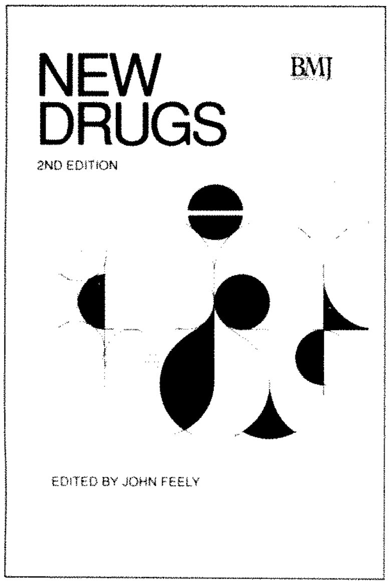

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The Varieties and Incidence of Pro-arrhythmias
Adverse Pro-arrhythmic Events as a Safety Concern in Clinical Trials

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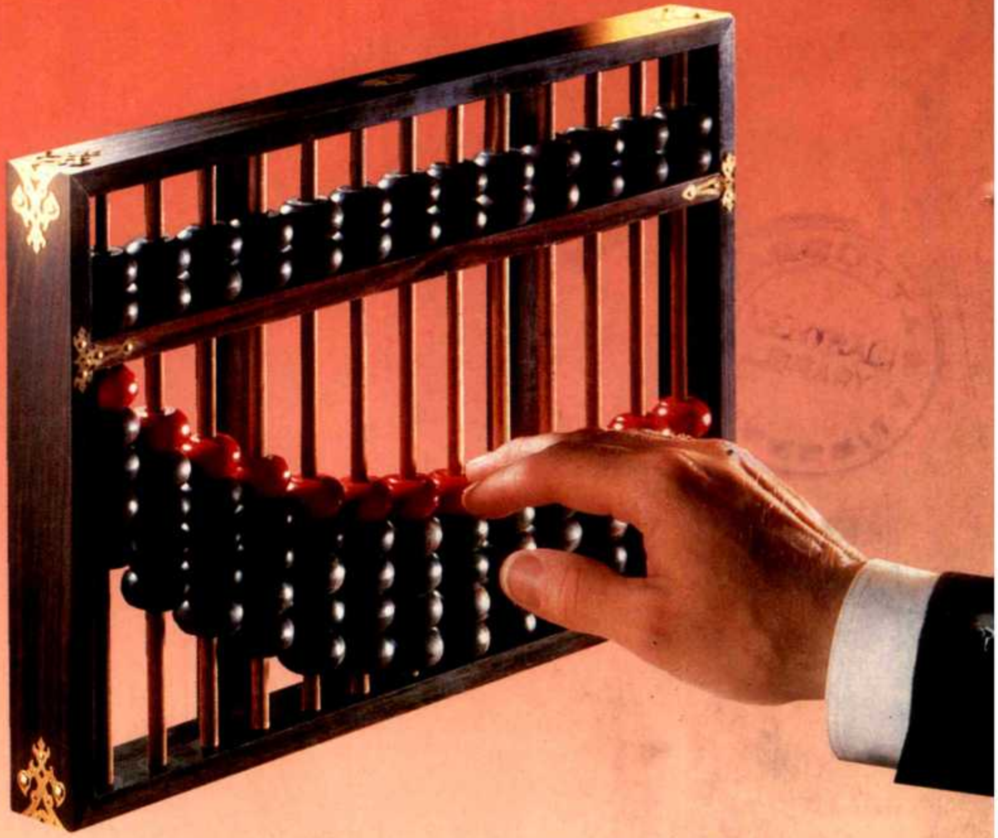

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Tenif

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Elderly Patients: Dosage should not exceed one capsule daily.

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Hepatic or renal impairment: In patients with marked renal impairment (ie. creatinine clearance below 15ml/min/1.73m^2, serum creatinine greater than 600 micromol/litre) the use of 'Tenif' is considered inappropriate. Care should be taken in patients with marked hepatic impairment.

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Product licence number and basic NHS cost: (29/0202), 28 capsules (OP) £10.90.

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BRITISH HEART JOURNAL

In association with the British Cardiac Society

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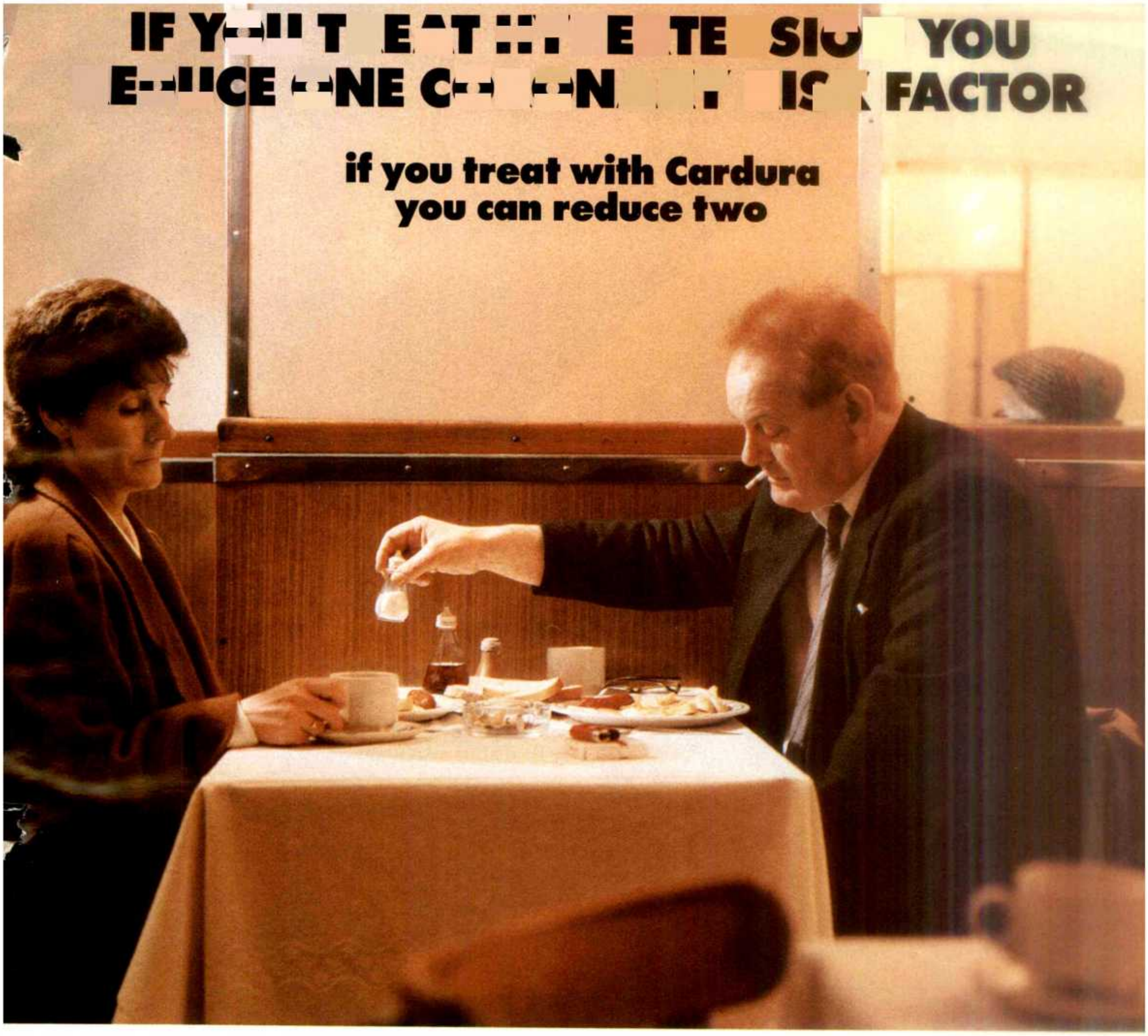
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55498

ABRIDGED PRODUCT INFORMATION

Refer to Data Sheet before prescribing.

INDICATIONS

Primary hypercholesterolaemia, intolerant or not responsive to other forms of therapy, with a cholesterol level in excess of 7.8 mmol/litre.

DOSAGE AND ADMINISTRATION

Initially 10 mg *nocte*; dose range 10-40 mg once daily *nocte*. Maximum therapeutic response occurs within four to six weeks. Consider dose reduction if total serum cholesterol level falls below 3.6 mmol/l or if LDL cholesterol falls below 1.94 mmol/l. (See Data Sheet for full dosage instructions.) A standard cholesterol-lowering diet should be continued. *Concomitant therapy:* 'Zocor' is effective alone or in combination with bile-acid sequestrants. *Impaired renal function and elderly patients:* Modification of dose should not be necessary. *Children:* Studies to show safety and efficacy have not been done.

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Hypersensitivity to this product; active liver disease or unexplained persistent elevations of serum transaminases; pregnancy and breast-feeding; women of child-bearing potential unless adequately protected by non-hormonal methods.

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BRITAIN TAKE HEART

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Reducing cholesterol to help reduce coronary risk

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0 mg tablets, £18.29 for 28-tablet calendar pack. 20 mg tablets, £31.09 for 28-tablet endar pack.

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EFERENCES

Study Group, *Europ. Heart J.*, 1987, **8**, 77.
Lipid Research Clinics Programme, *J. Amer. med. Ass.*, 1984, **251**, 351-364.
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Ref: 1 Singh BN et al. Am Heart J 1988; 116(6): 1542-1551 2 Ha Dinh et al. Am Heart J 1988; 115(1): 92-96

ABBREVIATED PRESCRIBING INFORMATION Presentation White, film coated 150mg and 300mg tablets containing propafenone hydrochloride. **Indications** Prophylaxis and treatment of ventricular arrhythmias. **Dose** Individual maintenance dose should be determined under cardiological surveillance and hospital conditions. **Adults** Initially 150mg three times daily increasing at a minimum of 3 day intervals to 300mg twice daily and, if necessary, to a maximum of 300mg three times daily. **Elderly patients; patients with impaired hepatic or renal function** A reduction in the recommended dose is advisable. **Contraindications** Uncontrolled heart failure, cardiogenic shock (except arrhythmia induced), severe bradycardia, uncontrolled electrolyte disturbances, severe obstructive pulmonary disease, marked hypotension, myasthenia gravis. Unless adequately paced, ARYTHMOL should not be used in the presence of sinus node dysfunction, atrial conduction defects, second degree or greater atrioventricular block, bundle branch or distal block. **Precautions** The minor negative inotropic effect of ARYTHMOL may assume importance in patients predisposed to heart failure. Caution should be exercised in patients with obstructive airways disease. Effects of ARYTHMOL may be potentiated if given with other local anaesthetic type agents or agents which depress myocardial activity. Reduced doses of digoxin, warfarin, propranolol and metoprolol may be required when given in combination with ARYTHMOL. Plasma levels of ARYTHMOL may be increased by concomitant administration of cimetidine or quinidine. Concomitant administration of rifampicin may reduce the plasma levels of ARYTHMOL resulting in a risk of breakthrough arrhythmias. ARYTHMOL has been shown to decrease pacemaker sensitivity and increase pacing thresholds. ARYTHMOL should not be used during pregnancy. **Side effects** Generally well tolerated. Minor side effects at high doses usually relate to the nervous system and cardiovascular system. Dizziness, nausea, vomiting, fatigue, bitter taste, constipation, diarrhoea, headache, blurred vision, dry mouth may occur. More rarely, bradycardia, sinoatrial, atrioventricular or intraventricular conduction blocks and hypotension may occur. Small risk of pro-arrhythmic effects. Very rarely hypersensitivity reactions (e.g. skin rash, cholestasis, blood dyscrasias, lupus syndrome) and seizures may occur. All side effects are reversible on discontinuation of treatment. **Product licence numbers** ARYTHMOL tablets 150mg 0169/0015, ARYTHMOL tablets 300mg 0169/0016. **Basic NHS price** ARYTHMOL 150mg × 90 – £19.98, ARYTHMOL 300mg × 60 – £19.98. Further information available from Knoll Ltd, Fleming House, 71 King Street, Maidenhead, Berkshire SL6 1DU.

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Br Heart J 1991;66:1–2

BRITISH
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Editorial

HIV cardiomyopathy: A dark cloud with a silver lining?

A wide variety of cardiac problems have been reported in patients infected with the human immunodeficiency virus (HIV). These include pericardial effusion, pulmonary hypertension and right heart failure, infective endocarditis, and tumours such as lymphoma and Kaposi's sarcoma.[1] However, left ventricular dysfunction caused by myocarditis or cardiomyopathy is emerging as the most important cardiac manifestation of HIV infection.[2]

Retrospective analysis of necropsy studies showed evidence of clinically unsuspected dilated cardiomyopathy in up to 25%[2] and of myocarditis in up to 52%[3] of patients with the acquired immunodeficiency syndrome (AIDS). Similarly, echocardiography showed impaired myocardial function in up to 75% of patients with AIDS.[4] The reported incidence of these phenomena varies widely, probably reflecting differences in methodology as well as the patients' risk group, stage of disease, and local environmental factors; nevertheless, it seems that HIV cardiomyopathy is a common condition in the later stages of the disease and that it affects patients in all major risk groups.[5]

The increasing success in combating opportunistic infections and slowing the progress of HIV disease itself may mean that many patients who otherwise would have died of non-cardiac illnesses will now survive to develop HIV cardiomyopathy. Indeed, end-organ failure and tumours are likely to become the predominant causes of death in patients infected with HIV. This, combined with the predicted rise in the number of infected individuals, particularly heterosexuals, is likely to lead to a substantial increase in the incidence of HIV cardiomyopathy.

In our experience HIV related myocardial dysfunction may easily be overlooked because of the tendency to attribute symptoms such as breathlessness and fatigue to respiratory disease or anaemia. If nothing else, this denies the victim the opportunity of palliative treatment. The diagnosis is readily made by echocardiography which can show dilatation or impaired contractility or both of either or both ventricles. While isolated right ventricular dysfunction can be caused by cardiomyopathy, it can also be caused by pulmonary hypertension secondary to repeated respiratory infections,[6] thromboembolic disease, or recurrent pulmonary emboli from intravenous debris acquired through drug abuse.

Endomyocardial biopsy in patients with heart failure associated with HIV infection has been performed in several centres and has identified myocarditis caused by potentially treatable infections with organisms such as *Toxoplasma gondii*.[7] The value of cardiac tissue obtained by these means is likely to be enhanced by the application of techniques such as the polymerase chain reaction and in situ hybridisation, which can be used to detect the presence of opportunistic organisms and the human immunodeficiency virus itself.

The pathogenesis of HIV cardiomyopathy, particularly its relation to myocarditis, has not been established. However, it seems likely that myocarditis acts as the substrate for the development of HIV cardiomyopathy and that the two conditions form a continuum. Necropsy studies in patients with HIV cardiomyopathy have shown huge variations in the prevalence of concomitant myocarditis.[3 8] This may reflect sampling errors, the difficulty of applying diagnostic criteria based on the combination of myocyte necrosis and an inflammatory infiltrate when the ability to mount an inflammatory response is impaired, and differences in the stage of disease.

Myocarditis may be caused by cell damage caused by activation of the immune system; by opportunistic infection with organisms such as *Aspergillus fumigatus*,[9] cytomegalovirus,[10] and *Cryptococcus neoformans*[11]; or by the human immunodeficiency virus itself.[12]

Activation of the humoral and/or cellular limbs of the immune system may cause damage directly,[3] or by means of a bystander effect,[13] where non-infected cells are destroyed by cytotoxic agents released during the course of an immune response directed against an infected minority cell population (for example, macrophages, T lymphocytes). Autoimmune damage may also occur as a result of alterations in the structure or expression of cardiac antigens.[14] Finally, some of the agents used to treat HIV associated opportunistic infection or retard the progression of the disease itself may be cardiotoxic; for example, pentamidine has been associated with malignant ventricular arrhythmias.[15] HIV cardiomyopathy probably represents the end stage of various insults operating concurrently and perhaps synergistically. Clearly there is a need to perform prospective studies to establish the true incidence, pathogenesis, and natural history of the condition.

The relation between myocarditis and idiopathic dilated cardiomyopathy is uncertain though the cardiomyopathy may develop from myocarditis. A similar sequence may occur in HIV myocardial disease. The scourge of syphilis in the early part of this century led to greater understanding of the pathophysiology of cardiovascular disease. HIV cardiomyopathy offers a similar opportunity to unravel the pathogenesis of idiopathic dilated cardiomyopathy. Although HIV cardiomyopathy may not have a unified aetiology, it occurs in a well-defined group of patients who can be studied premorbidly, and the associated viral antigens are highly characterised. We have, therefore, an exciting chance to document the natural history of a new disease and correlate this with external risk factors, individual susceptibility, and immunological events in blood and cardiac muscle.

HIV cardiomyopathy is a dark cloud that threatens to become an ever increasing problem, presenting cardiologists with considerable clinical challenges. This will be tempered by a silver lining of opportunities to enhance our knowledge of the mechanisms underlying idiopathic dilated cardiomyopathy.

A J J is supported by the British Heart Foundation.

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N A BOON

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1 Acierno LJ. Cardiac complications in acquired immunodeficiency syndrome (AIDS) a review *J Am Coll Cardiol* 1989;13 1144–54
2 Anderson DW. Emerging patterns of heart disease in human immunodeficiency virus infection *Hum Pathol* 1990;21 253–9.
3 Anderson DW, Virmani R, Reilly JM, *et al.* Prevalent myocarditis at necropsy in the acquired immunodeficiency syndrome *J Am Coll Cardiol* 1988,11 792–9
4 Baroldi G, Corallo S, Moroni M, *et al* Focal lymphocytic myocarditis in acquired immunodeficiency syndrome (AIDS) a correlative morphologic and clinical study in 26 consecutive fatal cases *J Am Coll Cardiol* 1988;12:463–9
5 Corallo S, Mutinelli MR, Moroni M, *et al* Echocardiography detects myocardial damage in AIDS. prospective study in 102 patients. *Eur Heart J* 1988,9 887–92.
6 Himelman RB, Dohrmann M, Goodman P, *et al.* Severe pulmonary hypertension and cor pulmonale in the acquired immunodeficiency syndrome. *Am J Cardiol* 1989;64:1396–9.
7 Grange F, Kinney EL, Monsuez J-J, *et al* Successful therapy for toxoplasma gondii myocarditis in acquired immunodeficiency syndrome. *Am Heart J* 1990;120 443–4.
8 Lewis W AIDS· cardiac findings from 115 autopsies. *Prog Cardiovasc Dis* 1989,32·207–15
9 Cox JN, di Dio F, Pizzolato G-P, Lerch R, Pochon N Aspergillus endocarditis and myocarditis in a patient with the acquired immunodeficiency syndrome (AIDS) *Virchows Arch [A]* 1990;417:255–9.
10 Stewart JM, Kaul A, Gromisch DS, *et al.* Symptomatic cardiac dysfunction in children with human immunodeficiency virus infection. *Am Heart J* 1989,117:140–4
11 Lafont A, Wolff M, Marche C, Clair B, Regnier B Overwhelming myocarditis due to cryptococcus neoformans in an AIDS patient. *Lancet* 1987,ii:1145–6
12 Grody WW, Cheng L, Lewis W Infection of the heart by the human immunodeficiency virus. *Am J Cardiol* 1990,66.203–6.
13 Ho DD, Pomerantz RJ, Kaplan JC. Pathogenesis of infection with human immunodeficiency virus. *N Engl J Med* 1987;317 278–86.
14 Cotton P. AIDS giving rise to cardiac problems *JAMA* 1990;263·2149.
15 Stein KM, Haronian H, Mensah GA, Acosta A, Jacobs J, Kligfield P. Ventricular tachycardia and torsades de pointes complicating pentamidine therapy of pneumocystis carinii pneumonia in the acquired immunodeficiency syndrome. *Am J Cardiol* 1990;66·888–9

Zestril
lisinopril ICI

Prescribing Notes.

Consult data sheet before prescribing.

Use: All grades of essential hypertension and renovascular hypertension. Congestive heart failure (adjunctive therapy).

Presentation: Tablets containing 2.5mg, 5mg, 10mg or 20mg lisinopril ('Zestril').

Dosage and administration: Hypertension – initially 2.5mg daily, a 2.5mg dose seldom achieves a therapeutic response; adjust dose according to response. Maintenance usually 10-20mg once daily. Maximum is 40mg daily. Diuretic-treated patients – if possible stop diuretic 2-3 days before starting 'Zestril'. Resume diuretic later if desired.

Congestive heart failure: (adjunctive therapy) – initially 2.5mg daily in hospital under close medical supervision, increasing to 5-20mg once daily according to response.

Impaired renal function: May require a lower maintenance dose. 'Zestril' is dialysable.

Elderly patients: No change from standard recommendations.

Contraindications: Pregnancy – stop therapy if suspected. Hypersensitivity to 'Zestril'. Patients reacting with angioneurotic oedema to previous ACE inhibitor treatment.

Precautions: Assessment of renal function is recommended. Renal insufficiency; renovascular hypertension; surgery/anaesthesia; possibility of hypotension especially in ischaemic heart disease and cerebrovascular disease. Combination with antihypertensives may increase hypotensive effect. Sometimes increased blood urea and creatinine and/or cases of renal insufficiency if given with diuretics. Minimises thiazide-induced hypokalaemia and hyperuricaemia. Potassium supplements, potassium-sparing diuretics and potassium-containing salt substitutes not recommended. Indomethacin may reduce hypotensive effect. Possible reduced response in Afro-Caribbean patients. Use with caution in breastfeeding mothers. Do not use in aortic stenosis or outflow tract obstruction or cor pulmonale. Monitor lithium serum levels if lithium salts administered.

Side effects: Dizziness, headache, diarrhoea, fatigue, cough and nausea. Less frequently, rash and asthenia. Rarely, angioneurotic oedema and other hypersensitivity reactions; renal failure; symptomatic hypotension (especially if volume-depleted); severe hypotension (more likely if severe heart failure); palpitation; hyperkalaemia; increases in liver enzymes and serum bilirubin (usually reversible on discontinuation of 'Zestril') and impotence.

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Br Heart J 1991;**66**:3–6

ORIGINAL ARTICLES

Outcome of extensive coronary artery dissection during coronary angioplasty

Tim R Cripps, John M Morgan, Anthony F Rickards

Abstract

A total of 32 (3·6%) patients of 880 undergoing coronary angioplasty during a nine year period at one hospital had extensive dissection (defined as a dissection extending beyond the limits of the dilated angioplasty balloon) in the coronary artery in which the angioplasty procedure was performed. Two (6·25%) of the 32 patients (both of whom were undergoing angioplasty because of unstable angina that was refractory to medical treatment) died as a consequence of the coronary artery dissection. Twelve (38%) needed immediate coronary artery bypass surgery and 11 (34%) had a myocardial infarction, which in four was minor in extent. During follow up, 20 of the 32 patients were successfully managed by medical treatment; only two needed further angioplasty procedures. There were no late deaths. Extensive coronary artery dissection is a serious complication of coronary angioplasty, with a high early mortality and a high incidence of infarction and requirement for bypass surgery. None the less, patients with extensive dissection who are free from the manifestations of acute ischaemia at the end of the procedure can be managed conservatively and have a good immediate and medium term outlook. Attempts should be made to stabilise extensive dissection during coronary angioplasty so that surgical intervention can be delayed or avoided altogether if possible.

Coronary artery dissection is a well recognised complication of coronary angioplasty.[1] The dissection may be localised at the dilatation site or may extend distally along the length of the arterial lumen.

Though localised dissection and plaque splitting are probably important mechanisms underlying successful dilatation[2] most acute ischaemic complications of coronary angioplasty are associated with an intimal tear.[3–5]

Several studies have been directed towards establishing an association between the occurrence of localised dissection and vessel occlusion, but few have focused on major dissections that extend beyond the length of the angioplasty balloon.

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Patients and methods

From 1980 to 1989, 880 patients were recorded as undergoing coronary angioplasty at the National Heart Hospital, London. A computer based search found that 32 patients had had extensive coronary artery dissection during the angioplasty procedure. This excluded those in whom dissection occurred during recanalisation of an occluded vessel ($n = 2$) or in whom dissection was caused during manipulation of the guiding catheter ($n = 1$).

Extensive dissection was defined as angiographic evidence of dissection extending beyond the segment of arterial wall that was contiguous with the fully dilated angioplasty balloon.

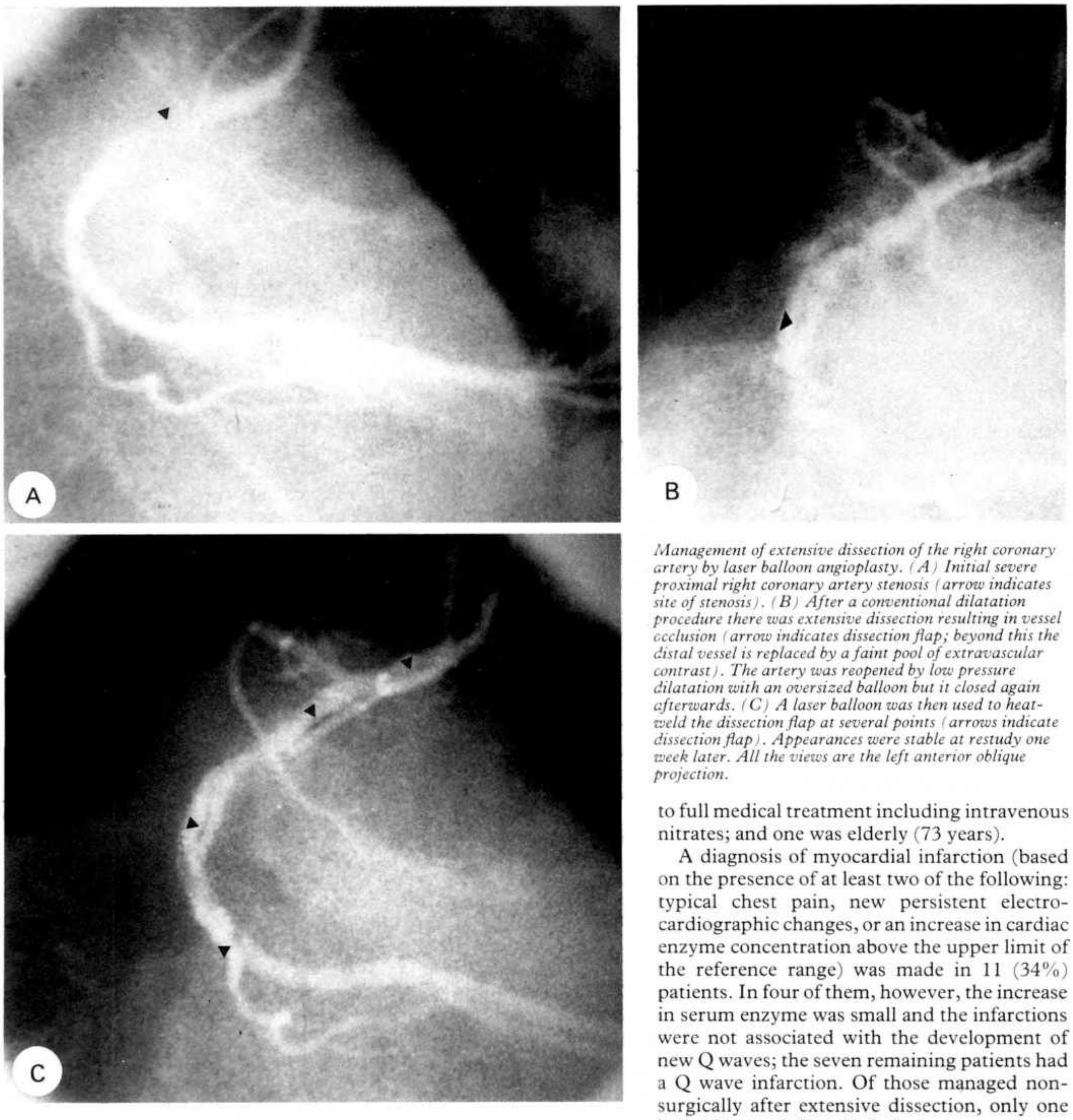
Of these 32 patients, 27 (84%) were men and 5 (16%) were women. Their mean age was 57 years (median 57 years, range 25–81). The procedure was performed in 25 (78%) patients with chronic stable angina, in five (16%) with unstable angina or evolving acute myocardial infarction, and in two (6%) for other reasons (after infarction in one patient aged 25 and during an evolving acute infarct in another).

Three patients had undergone one earlier coronary artery bypass operation; in one patient, surgery had been performed on two occasions. In three patients an earlier angioplasty had been performed.

Percutaneous transluminal angioplasty was performed with standard techniques and equipment. The femoral approach was used in all patients. β Blockers were stopped for 24 hours and aspirin given on the evening before the procedure. Intravenous heparin, 100 U/kg, was given routinely at the start and calcium antagonists were started after the procedure. Other antianginal agents were introduced subsequently as clinically indicated.

The policy on emergency surgery was as follows. When dissection occurred an attempt was made to "tack back" the dissection by long duration, low pressure inflations, often with an oversized balloon. When this approach was not successful, the patient was transferred for immediate surgery if there was continuing chest pain and electrocardiographic evidence of myocardial ischaemia, or haemodynamic instability. All patients who were managed medically had evidence of distal coronary flow at the end of the procedure.

Towards the end of the study period, balloon laser angioplasty and the intracoronary stent became available. These techniques were used only when the conventional tacking back



Management of extensive dissection of the right coronary artery by laser balloon angioplasty. (A) Initial severe proximal right coronary artery stenosis (arrow indicates site of stenosis). (B) After a conventional dilatation procedure there was extensive dissection resulting in vessel occlusion (arrow indicates dissection flap; beyond this the distal vessel is replaced by a faint pool of extravascular contrast). The artery was reopened by low pressure dilatation with an oversized balloon but it closed again afterwards. (C) A laser balloon was then used to heat-weld the dissection flap at several points (arrows indicate dissection flap). Appearances were stable at restudy one week later. All the views are the left anterior oblique projection.

procedures had failed and where there was continuing ischaemia, in other words, in those patients who otherwise would have proceeded to emergency surgery.

Results

One artery was dissected in each of the 32 patients. The artery affected was the left anterior descending in 17 (53%), the right coronary artery in 11 (34%), the circumflex branch of the left coronary artery in three (9%), and a saphenous vein bypass graft to the right coronary artery in one (3%) patient.

Two patients (6·25%) died as an early consequence of the coronary arterial dissection despite early emergency bypass surgery. The two patients who died were clinically unstable before the procedure, with prolonged spontaneous ischaemic episodes unresponsive to full medical treatment including intravenous nitrates; and one was elderly (73 years).

A diagnosis of myocardial infarction (based on the presence of at least two of the following: typical chest pain, new persistent electrocardiographic changes, or an increase in cardiac enzyme concentration above the upper limit of the reference range) was made in 11 (34%) patients. In four of them, however, the increase in serum enzyme was small and the infarctions were not associated with the development of new Q waves; the seven remaining patients had a Q wave infarction. Of those managed non-surgically after extensive dissection, only one had a Q wave infarct (inferior).

Immediate surgery was undertaken in 12 (38%) patients, because of continuing evidence of ischaemia, which could not be controlled by angioplasty techniques. The 12 patients included the two referred to above, who did not survive the operation. The remaining 10 patients survived the follow up period. Six of the 12 patients (including the two who died) who did have surgery had a Q wave infarction despite surgical intervention. This confirms that emergency surgery does not necessarily prevent myocardial infarction. In none of the patients was graft placement complicated by the presence of coronary artery dissection.

In all the patients, attempts were made first to stabilise the dissection medically, by the conventional approach of long duration, low pressure inflations, with an oversized angioplasty balloon. This was unsuccessful in all 12 of those who proceeded to emergency surgery and in two others—one in whom a laser balloon angioplasty device (USCI) was used to heat-weld the dissection flap (figure) and another in whom an intracoronary self-expanding stent (Medinvent)[6] was inserted to restore distal perfusion. In the remainder, tacking back was successful to a variable extent, but in all of them there was perfusion of the distal vessel at the end of the procedure.

Follow up continued (in those who survived the procedure and did not require surgery) for a mean of 19 months (median 7 months, range 1–50). No patient was lost to follow up, and no patient died during long term follow up. Two patients had elective surgery two months after the initial procedure for continuing disabling anginal symptoms that were unresponsive to medical treatment.

Of the 20 patients (63%) who survived the initial procedure and did not undergo surgery, three (15%) have grade III angina (Canadian Cardiovascular Society Classification) on medical treatment, but the other 17 have either no angina or minimal symptoms only.

Angiographic follow up was obtained in 12 patients. The figure shows an example of one such patient with a persistent stable coronary artery dissection. In seven of these 12 patients follow up angiography showed that the dissected vessel was patent.

Discussion

Extensive coronary artery dissection arising during the course of coronary angioplasty is a serious complication with a relatively high incidence of death, myocardial infarction, and the need for emergency coronary artery bypass surgery. We found, however, that in those patients with angiographically stable appearances with distal vessel perfusion and no ischaemic manifestations at the end of the procedure even extensive dissection was well tolerated in both the short and medium term so that immediate surgical intervention was not required.

It has been recognised for many years that localised dissection is a common finding after angioplasty, and that such localised intimal disruption usually heals well.[7] Some degree of intimal disruption and plaque splitting may well underlie a successful angioplasty result.[2] None the less, in some patients dissection is associated with serious ischaemic complications including vessel occlusion.

Murphy *et al* found that 12 (70%) of 17 patients who needed surgery because of refractory ischaemia after angioplasty had coronary dissection.[3] In another report 14 (70%) of 20 patients in whom acute occlusion developed after angioplasty had an intimal tear.[8] In a report of 500 consecutive procedures performed in Geneva, there were 30 acute occlusions, of which 21 (70%) showed evidence of dissection at the end of the procedure.[9] Bredlau *et al* reported a 6·5 fold increase in the risk of a major complication (emergency surgery, myocardial infarction, or death) when there was angiographic evidence of an intimal dissection, while the major complication rate in those without dissection was only 1·6%.[4]

Shiu *et al* found angiographic evidence of dissection in six out of 20 patients with total occlusions, four of whom required surgery; one of those managed medically died, though the other had a successful result and repeat angiography showed healing of the dissection.[10]

Few previous reports focused on the consequences of major dissection, the angiographic appearances of which may be alarming (figure). In one such report, Black *et al* found that the dissection length was related to the occurrence of complications (ischaemic chest pain, myocardial infarction, need for bypass surgery, or death) late after the procedure (after the patient had left the laboratory), but their study included only seven patients of the type forming the basis of our report (tear > 15 mm) and four of them had ischaemic complications.[1]

We found that two thirds (20/32) of the patients with extensive dissection survived without surgical intervention, with evidence of Q wave myocardial infarction in only one patient, who had an inferior infarct. None of these 20 patients managed without surgery required bypass surgery during follow up, and 17 now have no symptoms or mild angina only.

On the other hand, the seriousness of dissection should not be underestimated. The overall mortality in our series was 6·25%, and 38% of patients required bypass surgery. These figures are higher than would be expected for uncomplicated angioplasty procedures.[4] Furthermore, though 20 patients survived to long term follow up, three have significant angina on full medical treatment and may require further intervention in the future.

Coronary artery bypass surgery can be complicated in patients with extensive coronary artery dissection by the need to re-establish the true lumen.[11] There is a risk of placing a graft in the subintimal plane. Bypass grafting was achieved without difficulty in all of our operated cases.

The conventional treatment for coronary artery dissection occurring during coronary angioplasty is to attempt to tack back the dissection flap by long duration low pressure inflations often with an oversized angioplasty balloon.[12 13] This approach was successful in about half of our cases. In two patients in the later part of the series, however, novel approaches were used in patients who otherwise would have required surgery. In one, laser balloon angioplasty was used to stabilise the dissection and in the other an intracoronary stent was inserted. In both, the symptomatic and angiographic results were excellent and surgical intervention was avoided. The application of such novel methods may allow even more patients with extensive dissection to be managed conservatively. Immediate surgery for acute dissection is essential where ischaemia persists despite attempts to stabilise the patient non-surgically but in many cases it seems that it is possible to stabilise the dissection by angioplasty techniques, and in our experience the outcome is good in such cases. It may be that with increased use of adjuncts to conventional angioplasty, including intracoronary stents[6] and the laser balloon[14] the proportion of patients requiring emergency surgical intervention can be further reduced.

Extensive coronary artery dissection is a serious complication of coronary angioplasty, with a high mortality, incidence of myocardial infarction, and requirement for immediate bypass surgery. However, most patients who suffer this complication seem to do well in the medium term with conservative management; this allows elective surgical intervention to be considered.

TRC was supported by the Charles Wolfson Charitable Trust.

1 Black AJR, Namay DL, Niederman AL, *et al.* Tear or dissection after coronary angioplasty. Morphologic correlates of an ischaemic complication. *Circulation* 1989;79:1035–42.

2 Block PC, Myler RK, Stertzer S, Fallon JT. Morphology after transluminal angioplasty in human beings. *N Engl J Med* 1981,305:382–5.

3 Murphy DA, Craver JM, Jones EL, *et al.* Surgical revascularization following unsuccessful percutaneous transluminal coronary angioplasty. *J Thorac Cardiovasc Surg* 1982,84:342–8.

4 Bredlau CE, Roubin GS, Leimgruber PP, *et al.* In-hospital morbidity and mortality in patients undergoing elective coronary angioplasty *Circulation* 1985;72:1044–52

5 Ellis SG, Roubin GS, King SB, *et al.* Angiographic and clinical predictors of acute closure after native vessel coronary angioplasty *Circulation* 1988;77:372–9.

6 Sigwart U, Puel J, Mirkovitch V, Joffre F, Kappenberger L Intravascular stents to prevent occlusion and restenosis after coronary angioplasty. *N Engl J Med* 1987;316:701–6

7 Dorros G, Spring DA Healing of coronary artery intimal dissection after percutaneous transluminal angioplasty [Abstract] *Am J Cardiol* 1980;45.423.

8 Hollman J, Gruentzig AR, Douglas JS, *et al* Acute occlusion after percutaneous transluminal coronary angioplasty—a new approach. *Circulation* 1983;68.725–32.

9 Steffenino G, Meier B, Finci L, *et al* Acute complications of elective coronary angioplasty: a review of 500 consecutive procedures. *Br Heart J* 1988,59:151–8

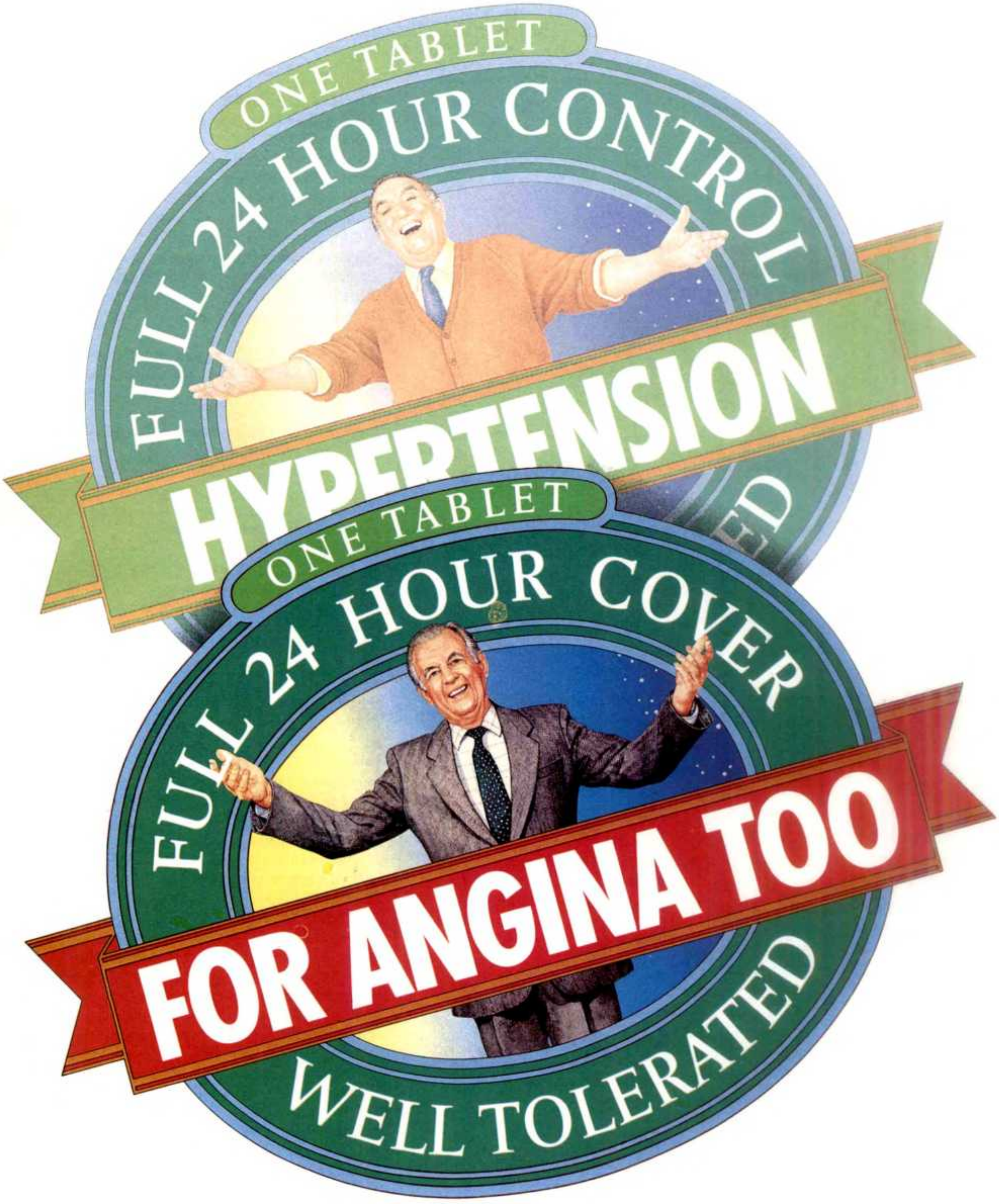
10 Shiu MF, Silverton NP, Oakley D, Cumberland D. Acute coronary occlusion during percutaneous transluminal coronary angioplasty. *Br Heart J* 1985,54:129–33

11 Phillips SJ, Kongtahworn C, Zeff RH, *et al.* Disrupted coronary artery caused by angioplasty: supportive and surgical considerations. *Ann Thorac Surg* 1989,47:880–3.

12 Marquis J-F, Schwartz L, Aldridge H, *et al.* Acute coronary artery occlusion during percutaneous transluminal coronary angioplasty treated by redilation of the occluded segment. *J Am Coll Cardiol* 1984;4:1268–71

13 Simpendorfer C, Belardi J, Bellamy G, *et al.* Frequency, management and follow-up of patients with acute coronary occlusions after percutaneous transluminal coronary angioplasty *Am J Cardiol* 1987;59 267–9.

14 Hiehle JF, Bourgelais DBC, Shapshay S, *et al.* Nd-YAG laser fusion of human atheromatous plaque-arterial wall separations in vitro. *Am J Cardiol* 1985,56:953–7.



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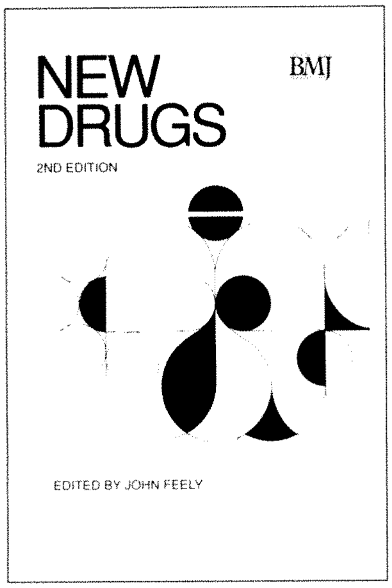

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References
1. Kjekshus, J., and Swedberg, K., *Amer. J. Cardiol.*, 1989, **63**, 26D.
2. Swedberg, K., and Kjekshus, J., *Drugs*, 1990, **39** (Suppl. 4), 49.
3. CONSENSUS Trial Study Group, *New Engl. J. Med.*, 1987, **316**, 1429.

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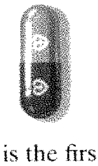

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Br Heart J 1991;66:7–9

Plasma endothelin in coronary venous blood from patients with either stable or unstable angina

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Abstract

Study objective—**To test the hypothesis that the active coronary endothelial lesions in unstable angina raise the endothelin concentration in coronary venous blood.**

Design—**Systemic and coronary venous blood samples were obtained from unselected patients with the clinical syndromes of either stable or unstable angina at the time of cardiac catheterisation and coronary arteriography. Control venous blood samples were obtained from healthy laboratory workers and from patients with chronic renal failure treated by intermittent haemodialysis.**

Patients—**Twelve patients with angina: seven with stable symptoms and five with unstable angina.**

Results—**The mean coronary venous endothelin concentration in unstable angina was 2·32 ng/l (range 1·7–3·2 ng/l). In stable angina it was 2·77 ng/l (range 2·1–4·4 ng/l). These values were not significantly different from one another nor from the values obtained in systemic venous blood from either group or from the healthy controls. Circulating endothelin concentrations were much higher in venous blood from the patients treated by haemodialysis.**

Conclusions—**These data do not support the hypothesis that raised endothelin concentrations in coronary blood in patients with unstable angina may modulate variations in coronary arterial tone thereby contributing to the clinical syndrome of chest pain and electrocardiographic changes at rest. The raised endothelin concentrations seen in systemic venous blood after myocardial infarction may be part of the systemic response to myocardial infarction.**

There is increasing evidence that the vascular endothelium helps to regulate vascular smooth muscle tone. Endothelium dependent vasodilatation was first reported in 1980,[1] and a vasoconstrictor substance derived from cultured endothelial cells, now called endothelin, was reported some years later.[2-4] Although its exact physiological role is not yet known, endothelin mediated vasoconstriction may be induced by various hormonal, neural, and mechanical stimuli. Endothelin release is stimulated by, among other things, thrombin[4] and sheer stress,[5] suggesting that it may play a role in local haemostasis and implying that an important stimulus to its release is local endothelial cell injury. High circulating concentrations of endothelin have also been discovered in patients with acute renal failure[6] and in those with chronic renal failure receiving haemodialysis, but not in those with chronic renal failure who are not receiving dialysis.[7] Endothelial injury, particularly during haemodialysis, has been proposed as the explanation for this observation. The reported intraoperative increase in circulating endothelin concentrations in patients undergoing abdominal surgery was attributed to vascular endothelial cell injury during surgical manipulation.[8]

In acute coronary syndromes, including unstable angina, there is endothelial damage and thrombus formation in the coronary circulation.[9-11] On theoretical grounds such stimuli might be expected to stimulate endothelin production in the coronary circulation. If this were so, it might help to explain the apparently spontaneous variations in coronary tone seen in unstable angina and "stuttering myocardial infarction". Thus endothelin released locally as a result of endothelial injury and thrombus formation might influence symptoms and outcome in acute coronary syndromes.

Patients and methods

Endothelin concentrations were assayed in coronary sinus blood and in paired samples of systemic venous blood in 12 patients (eight men and four women, aged 40–73) with angina, at the time of cardiac catheterisation and coronary arteriography. Seven patients had chronic stable angina; in five of them (71%) there was multivessel coronary disease. The other five had unstable symptoms, with chest pain and ST segment depression at rest, from 4 to 24 hours before catheterisation; multivessel coronary disease was present in three (60%). All the patients with unstable angina were receiving intravenous nitrate and heparin infusions at the time of angiography. No patient, in either group, complained of angina during coronary arteriography. Informed consent was obtained before the procedure and all patients had been fasting for at least six hours before catheterisation was performed. The results were compared with endothelin concentrations assayed in samples of venous blood obtained from patients with chronic renal failure treated with regular haemodialysis.

Before angiography took place in 10

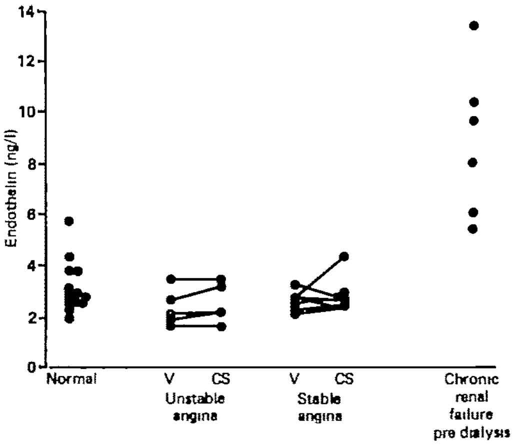
patients the coronary sinus was intubated with a polyethyline 7F Sones catheter (Cordis UK, Brentford, Middlesex), positioned from the left subclavian vein. In the remaining two patients, the coronary sinus was intubated with a woven Dacron thermodilution catheter (Webster Laboratories, Baldwin Park, California) approximately 10 minutes after coronary arteriography had been performed. In all patients the tip of the catheter was positioned approximately 2·5 cm from the os of the coronary sinus, to minimise the risk of admixture of right atrial blood in the samples; a satisfactory catheter position was confirmed by the hand injection of radiographic contrast.

Paired 8 ml samples of coronary venous and systemic venous (either right atrial or pulmonary arterial) blood were collected into refrigerated tubes containing sodium EDTA 1·5 mg/ml and aprotonin 500 KIU/ml and stored on ice. Samples were centrifuged at 2°C, separated within an hour of collection, and stored at −70°C for up to three months (two months on average). During this period venous blood was also collected from a group of healthy controls and from a group of patients with chronic renal failure, on a programme of regular haemodialysis.

Endothelin was assayed according to the Peninsula Laboratories' protocol, modified to increase sensitivity by extracting 4 ml plasma instead of 2 ml. Acidified plasma was applied to a C18 Sep column, and after this was washed with 0·1% trifluoroacetic acid endothelin-like materials were eluted with 60% acetonitrile in 0·1% trifluoroacetic acid. The eluant was evaporated to dryness and the residue was reconstituted in 0·6 ml of buffer. Endothelin was then measured with the Peninsula radioimmunoassay kit. Low concentration and high concentration quality control samples were prepared by adding endothelin to EDTA plasma, stored in aliquots at −70°C, and assayed in each batch throughout the study period. Recovery of endothelin throughout the entire procedure was assessed by the addition of 4 ng/l and 32 ng/l endothelin to EDTA plasma from healthy controls.

Results

The mean plasma endothelin concentration in coronary sinus blood in the patients with unstable angina was 2·32 ng/l (range 1·7–3·2), and in the patients with stable symptoms it was 2·77 ng/l (range 2·1–4·4 ng/l). These values were not significantly different from one another or from the mean values obtained in systemic venous blood—that is, 2·42 (range 1·9–3·5) ng/l and 2·57 (range 2·0–3·1) ng/l in the unstable and stable groups respectively. The endothelin values in systemic blood from the patient groups were similar to those found in 15 healthy laboratory workers (mean 3·0 ng/l, range 2·0–5·9). In contrast, circulating endothelin concentrations in the patients receiving haemodialysis for chronic renal failure were much higher, with a mean value of 8·4 ng/l (range 5·0–13·3 ng/l), which accords with that reported in such patients by other groups.[7] The figure shows the results.



Endothelin concentrations in systemic (V) and coronary (CS) venous blood in patients with unstable or stable angina and in systemic venous blood from healthy laboratory workers and from patients with chronic renal failure.

Recovery of added endothelin was 84% (range 75–89%, n = 6) and 98% (range 76–118%, n = 4) for the addition of 4 and 32 ng/l respectively. Endothelin values (mean (SD)) in the low concentration and high concentration quality control samples, analysed with each batch, were 7·85 (2·18) ng/l and 38·3 (8·0) ng/l respectively (n = 8). In the high concentration quality control sample, however, the endothelin values were approximately 30% lower after 7·5 months storage at −70°C.

Discussion

We did not show an increase in endothelin concentration in the coronary circulation or in the systemic circulation of patients with either stable or unstable angina. The kinetics of endothelin synthesis and release are such that we would have expected to detect raised concentrations in the coronary venous blood of these patients if endothelin-modulated variations in coronary arterial tone contributed to the chest pain and electrocardiographic changes of unstable angina.

These data must be interpreted in the light of recently published work from Yasuda *et al*, who showed raised plasma endothelin concentrations in systemic venous blood from nine patients with acute myocardial infarction but not from 10 patients with stable angina.[12] Endothelin concentration in venous blood was highest within 24 hours of myocardial infarction and fell gradually over a period of 14–16 days to the value found in controls who did not have coronary artery disease. In the infarct patients there was a significant association between plasma endothelin concentration and left ventricular wall motion abnormality, and between plasma endothelin concentration and systemic markers of activation of the coagulation system (thrombin-antithrombin III complex, and β-thromboglobulin), but not between endothelin concentration and systemic blood pressure. The highest concentrations seen, however, were in two patients in Killip subset

IV—that is in the two patients with the largest infarcts and greatest haemodynamic disturbance.

The source of the endothelin in the infarct patients was not identified, but the inference was that it arose in the coronary circulation. Unlike other vasoactive peptides found in the coronary circulation, endothelin is not stored in subcellular vesicles. This makes it unlikely that it could arise from lysed endothelial cells within the infarct, but stimulated endothelial cells in the border zone of the infarct are a possible source. Another possibility is that the endothelin was produced in extracardiac sites as part of the systemic response to myocardial infarction, perhaps secondary to the hypercoagulability and platelet hyperreactivity seen in acute myocardial infarction or to increased sympathetic activity. (The same group has published data showing that adrenaline increased endothelin production from cultured porcine endothelial cells[13].)

Yasuda *et al* speculated on the possible physiological or pathophysiological effects of endothelin in acute myocardial infarction. There may be a role for a powerful vasoconstricting and positively inotropic agent in the patient who is hypotensive after infarction, and, despite the lack of a significant association between endothelin concentration and systemic blood pressure in this study, the high concentrations in the two patients in Killip class IV are intriguing. Raised concentrations were found in patients with cardiogenic shock, whereas, in the same study, the concentrations in patients with stable congestive heart failure were not raised.[14] Our data, which show no increase in endothelin concentration in coronary sinus blood or systemic venous blood from patients with unstable angina pectoris support the contention that the raised endothelin production was part of the systemic response to acute myocardial infarction.

The assay showed the expected high concentrations of circulating endothelin in patients with chronic renal failure on haemodialysis, which suggests that the low concentrations measured in the patients with coronary artery disease were probably valid, although the quality control data showed that assay precision during the study was not good. The high concentration quality control sample seemed to be unstable, which casts doubt on the reliability of the data based on it, at least in the assessment of precision. No decrease in endothelin was seen for the low concentration quality control sample, but this could have been masked by imprecision. If there had been any loss in endothelin activity in the patients' samples it would not have explained our failure to detect a difference in endothelin concentration between venous and coronary sinus blood. Paired samples of systemic and coronary venous blood were stored for the same length of time and were analysed together in the same batch. It is still possible, however, that small increases in endothelin concentration in coronary sinus blood compared with systemic venous blood remained undetected by the methods we used. If this were so, a sensitive immunometric assay without column extraction would have been more appropriate.

Although endothelin is not available for immediate release, its synthesis in the face of endothelial injury seems to be rapid, as is its appearance in systemic blood after myocardial infarction.[12] We would expect, therefore, that patients with symptoms of unstable angina for several days and active intimal lesions would be producing endothelin. We were not able to show an increase in endothelin concentration in the coronary circulation, and it is still not certain whether endothelin helps to modulate coronary vasomotor tone in unstable angina pectoris. Its origin and its role in patients with acute myocardial infarction remain to be established.

1 Furchgott RF, Zawadzki JV. The obligatory role of endothelial cells in the relaxation of arterial smooth muscle by acetylcholine *Nature* 1980,288 373–6
2 Gillespie MN, Owasoyo JO, McMurtry IF, O'Brien RF Sustained coronary vasoconstriction provoked by a peptidergic substance released from endothelial cells in culture. *J Pharmacol Exp Ther* 1986;236 339–43
3 O'Brien RF, Robbins RJ, McMurtry IF. Endothelial cells in culture produce a vasoconstrictor substance *J Cell Physiol* 1987,132·263–70.
4 Yanagisawa M, Kurihara H, Kimura S, *et al*. A novel potent vasoconstrictor peptide produced by vascular endothelial cells. *Nature* 1988;332.411–5
5 Yoshizumi M, Kurihara H, Sugiyama T, *et al* Hemodynamic shear stress stimulates endothelin production by cultured endothelial cells. *Biochem Biophys Res Commun* 1989,161 859–64
6 Tomita K, Ujie K, Nakanishi T, *et al* Plasma endothelin levels in patients with acute renal failure *N Engl J Med* 1989,321 1127
7 Koyama H, Nishzawa Y, Morii H, Tabata T, Inoue T, Yamaji T Plasma endothelin levels in patients with uraemia *Lancet* 1989,i:991–2
8 Hirata Y, Itoh K-I, Ando K, Endo M, Marumo F Plasma endothelin levels during surgery. *N Engl J Med* 1989;321 1686
9 Davies MJ, Thomas AC. Plaque fissuring—the cause of acute myocardial infarction, sudden ischaemic death, and crescendo angina *Br Heart J* 1985,53 363–73.
10 Falk E Unstable angina with fatal outcome. dynamic coronary thrombosis leading to infarction and/or sudden death Autopsy evidence of recurrent mural thrombus with peripheral embolization culminating in total vascular occlusion *Circulation* 1985,71 699–708
11 Sherman CT, Litvak F, Grundfest W, *et al* Coronary angioscopy in patients with unstable angina pectoris *N Engl J Med* 1986,315 913–9
12 Yasuda M, Kohno M, Tahara A, *et al*. Circulating immunoreactive endothelin in ischemic heart disease *Am Heart J* 1990;119 801–6
13 Kohno M, Murakawa K, Yokokawa K, *et al*. Production of endothelin by cultured porcine endothelial cells—modulation by adrenaline *J Hypertens* 1989; 7(suppl 6) S130–1
14 Cernacek P, Stewart DJ. Immunoreactive endothelin in human plasma. marked elevations in cardiogenic shock *Biochem Biophys Res Commun* 1989,161 562–7.

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Thrombolytic treatment in acute myocardial infarction: neutrophil activation, peripheral leucocyte responses, and myocardial injury

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Abstract

Objective—To examine early leucocyte responses and neutrophil activation in acute myocardial infarction treated by streptokinase and to relate the findings to coronary recanalisation and indices of myocardial damage in order to provide further information about the role of neutrophils in the evolution of injury.

Design—Group analysis of paired blood samples, obtained before streptokinase treatment and one hour after it, and of three indirect measures of myocardial injury: left ventricular ejection fraction, QRS score, and peak creatine kinase.

Setting—The coronary care unit of a district general hospital.

Patients—39 patients with acute myocardial infarction who underwent paired blood sampling (before streptokinase and one hour after streptokinase) and cardiac catheterisation 5 (3–8) days later.

End points—Changes in peripheral white cell and neutrophil counts and plasma elastase one hour after streptokinase infusion. Comparison of these variables in patients with and without patency of the infarct related coronary artery. Correlations between these variables and indirect measures of myocardial injury.

Results—Neutrophil activation, as reflected by plasma elastase, increased sharply one hour after streptokinase. Total white cell and neutrophil counts also increased. Changes tended to be more pronounced in patients with patency of the infarct related artery, though the trend was not statistically significant. Neutrophil activation before streptokinase was unrelated to indirect indices of myocardial injury but only one hour after streptokinase a weak negative correlation with left ventricular ejection fraction had developed. Peripheral neutrophil responses showed a similar relation to ejection fraction and also correlated with peak creatine kinase and QRS score.

Conclusions—Thrombolytic treatment in acute myocardial infarction is associated with an abrupt reactive neutrophil response which provides an early measure of injury. It is also associated with neutrophil activation, probably in response to coronary recanalisation and myocardial reperfusion. Activated neutrophils are recognised as mediators of reperfusion injury in experimental infarction and the data in the present study provide preliminary evidence of a similar pathogenic role in the clinical setting.

The benefits of thrombolytic treatment for reducing mortality in acute myocardial infarction are well established[1–3] but residual left ventricular dysfunction usually persists even when thrombolysis is successful in restoring coronary patency.[4–8] Residual left ventricular dysfunction largely reflects damage incurred during the ischaemic period but damage at the time of reperfusion can also contribute.[9]

We have previously reported evidence that oxygen derived free radicals are generated in response to myocardial reperfusion in patients treated with streptokinase[10] and more recently we have provided preliminary data relating the free radical response to eventual infarct size.[11] Activated neutrophils are a potent source of oxygen derived free radicals and there is a large body of experimental data indicating that they may be important in the pathogenesis of reperfusion injury.[12 13] Neutrophil infiltration of the infarct territory can be shown within three to six hours of coronary occlusion and is particularly pronounced after reperfusion.[14] Reperfusion provokes various chemotactic mechanisms including the complement system and coagulation pathways[15] that activate neutrophils and lead to release of oxygen derived free radicals, arachidonic acid metabolites, and lysosomal enzymes all of which are toxic to vascular endothelium and cardiac myocytes and may contribute to the extension of myocardial injury.[16–18] Evidence for the pathogenic role of neutrophils in experimental reperfusion injury is strengthened by the demonstration of myocardial protection with neutrophil depleted perfusates or agents that suppress neutrophil chemotaxis.[19 20]

Despite the body of experimental data implicating neutrophils as mediators of reperfusion injury, clinical data are scarce and the importance of this mechanism in patients with acute myocardial infarction is unknown. The purpose of the present study, therefore, was to

Table 1 Data on patients

Variable	*Result*	
Number of patients	39	
Age (years) (median (range))	57	(47–67)
Sex:		
Male	29	
Female	10	
Infarct location:		
Anterior	18	
Inferior	21	
History of previous infarction	6	
Time to streptokinase (min) (median (range))	210	(165–348)
Time to cardiac catheterisation (days) (median (range))	5	(3–8)
Infarct related coronary artery:		
Recanalised	34	
Non-recanalised	5	
Coronary artery disease:		
1 Vessel	16	
2 Vessel	10	
3 Vessel	13	
Left ventricular ejection fraction (%) (median (range))	57	(47–67)

examine the interaction of thrombolytic treatment and neutrophil activation in patients with acute myocardial infarction and to relate the findings to coronary recanalisation and indices of myocardial damage in order to provide further information about the role of neutrophils in the pathogenesis of reperfusion injury.

Patients and methods

PATIENTS

We studied a consecutive series of 39 patients with acute myocardial infarction receiving thrombolytic treatment in whom we obtained a complete set of paired blood samples for white cell and neutrophil counts and plasma neutrophil elastase (table 1). All were treated with 1·5 MU of streptokinase infused intravenously over one hour. The median time from onset of continuous severe chest pain to start of streptokinase infusion was 210 (165–348) minutes.

BLOOD SAMPLING AND ANALYSIS

Paired venous blood samples were obtained immediately before thrombolytic treatment and again one hour after the streptokinase infusion. Samples were drawn without venous occlusion and anticoagulated in EDTA for measurement of total leucocyte and neutrophil counts and in citrate for measurement of plasma neutrophil elastase. Leucocytes and neutrophils were counted by a Coulter S + V1 automated blood cell counter. Samples for neutrophil elastase were centrifuged and the plasma frozen to −20°C within 30 minutes of the blood being drawn. The plasma samples were stored at −80°C for analysis in one batch. Neutrophil elastase was measured as elastase α_1 proteinase inhibitor complexes by a sensitive double antibody sandwich ELISA (Merck kit 15689 Immunoassay Polymorphonuclear Elastase). The detection limit of the test is approximately 0·25 ng elastase in complex bound form.

ELECTROCARDIOGRAPHIC AND ENZYMATIC DATA

Predischarge 12 lead electrocardiograms adequate for QRS scoring were obtained in 27 patients seven (range 5–9) days after admission. Scoring was by the 29 point system described by Palmeri *et al*[21] on the basis of the Q and R wave duration and the R to Q and R to S amplitude ratios. Blood samples for creatine kinase activity were obtained on admission to hospital, and on the next two consecutive mornings according to the policy of our coronary care unit. A complete set of three creatine kinase measurements was obtained in 29 patients.

CARDIAC CATHETERISATION

All patients gave written informed consent for coronary arteriography and single plane (right anterior oblique) left ventriculography. Studies were performed five (range 3–8) days after hospital admission to determine the patency of the infarct related coronary artery, the extent of associated coronary artery disease, and left ventricular function. Patency of the infarct related coronary artery was assessed by TIMI criteria.[2] Left ventriculograms suitable for quantitative analysis of ejection fraction by the method of Sandler and Dodge[22] were obtained in 31 patients. Of these, four had a history of previous Q wave infarction, leaving 27 studies suitable for assessment of myocardial injury in the present study.

STATISTICAL ANALYSIS

In all analyses, non-parametric (distribution free) statistics were used. Values were expressed as median with the interquartile range in parentheses. For unpaired comparisons we used the Mann-Whitney U test and for paired comparisons the Wilcoxon test. We used the Spearman rank correlation coefficient to examine correlations.

Results

BASELINE VALUES (TABLE 2)

Blood samples obtained at the time of admission, before treatment with streptokinase, showed modest increases in mean white cell and neutrophil counts. Plasma neutrophil elastase was also increased but showed no significant relation with the neutrophil count.

RESPONSES TO STREPTOKINASE (TABLE 2)

Coronary arteriography seven (5) days (mean (SD)) after streptokinase infusion showed that the infarct related artery was patent in 87% of patients. Only five patients had persistent coronary occlusion. The total white cell and neutrophil counts increased sharply an hour after streptokinase, with median values increasing by 43% and 69% respectively. A 45% increase in plasma elastase indicated

Table 2 Changes in white cells, neutrophils, and plasma neutrophil elastase before and one hour after streptokinase (median (range))

Variable	*Before streptokinase*		*1 h after streptokinase*		*p*
White cells (× 10^9/l)	11 5	(9 5–13 4)	16 5	(12 2–20 0)	<0 001
Neutrophils (× 10^9/l)	8 4	(6·1–10 4)	14 2	(10·1–18 3)	<0·001
Plasma neutrophil elastase (ng/ml)	56·1	(43 4–83·5)	81 6	(54 2–165·8)	<0·01

Table 3 Effects of recanalisation of the infarct related coronary artery on white cells, neutrophils, and neutrophil elastase before and after streptokinase

	Recanalised artery (n = 34)	*Not recanalised artery (n = 5)*
White cells (× 10^9/l)·		
Before streptokinase	11 8 (9 7–13 9)	11 0 (9 3–11 3)
After streptokinase	17 4 (12 6–20 8)	15 1 (9 9–16 4)
Difference	5 2 (2 1–7 8)	3 9 (0 7–4 9)
Neutrophils (× 10^9/l).		
Before streptokinase	8 4 (6 1–11 1)	8 4 (6 9–8 5)
After streptokinase	14·9 (10 1–18 6)	11 3 (8 0–13 9)
Difference	6 2 (3 2–9 3)	2 8 (1 8–5 8)
Plasma neutrophil elastase (ng/ml)		
Before streptokinase	59 9 (43·3–94 3)	53 5 (42 7–74 0)
After streptokinase	81 6 (56 1–176 0)	66 3 (45 2–81 6)
Difference	19 1 (0–84 2)	0 (– 12 8–28 7)

None of the differences between the group with recanalised arteries and the group without was statistically significant.

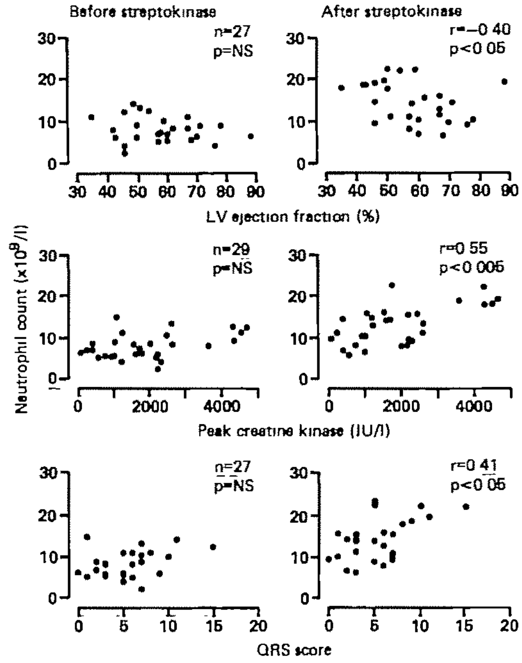


Figure 1 Relations between peripheral neutrophil counts and three indirect measures of myocardial injury before streptokinase treatment and one hour after it.

neutrophil activation. These changes were all highly significant but no differences could be shown between patients with a patent infarct related vessel and those without at five (3–8) days. Nevertheless, in those with early patency, white cell and peripheral neutrophil responses tended to be more vigorous, as did neutrophil activation (median values for plasma elastase increased by 32% after streptokinase infusion in patients with early coronary patency but showed no change in patients with persistent coronary occlusion (table 3).

NEUTROPHILS, NEUTROPHIL ELASTASE, AND MYOCARDIAL INJURY

The neutrophil count on admission, before streptokinase infusion, was unrelated to any of the indirect measures of myocardial injury. Only one hour after streptokinase, however, significant correlations with left ventricular ejection fraction, peak creatine kinase, and QRS score had developed (fig 1). Neutrophil activation, as reflected by plasma elastase, also correlated with left ventricular ejection fraction one hour after streptokinase infusion but not with the other indirect measures of myocardial injury (fig 2).

Discussion

Studies in which autologous neutrophils labelled with indium-111 were reinjected into patients with acute myocardial infarction indicated that the stimulus for neutrophil activation occurs early.[23 24] This is confirmed in the present study which showed an abrupt increase in plasma elastase within an hour of streptokinase infusion. The close temporal relation with administration of thrombolytic treatment suggests that reperfusion may be important in the activation process. Nevertheless, the trend towards a more vigorous elastase response in patients with patency of the infarct related artery was not statistically significant, possibly because of numerical imbalance between the groups (there were only five "occluded" cases) or delay before coronary arteriography. This will have led to random misclassification of some "patent" and "occluded" cases, so reducing the power of the statistical analysis.

Others reported increases in plasma elastase after thrombolytic treatment of acute infarction.[25 26] Bell *et al*, however, found no associated increase in the uptake of ^{111}I-labelled neutrophils in the infarcted myocardium and concluded that the elastase response was due to clot lysis or intracoronary (as opposed to intramyocardial) activation of neutrophils.[25] In experimental models of coronary occlusion, however, activated neutrophils accumulated very rapidly in the zone of infarction during reperfusion,[14] and if this occurs clinically in response to successful thrombolytic therapy it may well have contributed to the sharp increase in plasma elastase seen in this and other studies. Activated neutrophils were identified as a cause of reperfusion injury in experimental infarction and the present study suggests they may have a similar effect after thrombolytic treatment. Thus we were able to show a significant negative correlation between plasma elastase one hour after streptokinase and left ventricular ejection fraction; in patients with a more exaggerated elastase response left ventricular function was significantly more impaired. This indicates that neutrophil activation was, at least in part, related to the process of infarction and was not stimulated directly by streptokinase. Nevertheless, the correlation was weak and there was no significant relation with peak creatine kinase or QRS score, indicating that the contribution of neutrophil activation to infarction is likely to be small, particularly when compared with the effects of ischaemic injury.

An alternative explanation for the sharp rise in plasma elastase early after streptokinase infusion is washout from a previously unperfused myocardium. This would imply considerable accumulation of activated neutrophils in the zone of infarction early after coronary occlusion rather than their entry in response to reperfusion. A study such as ours

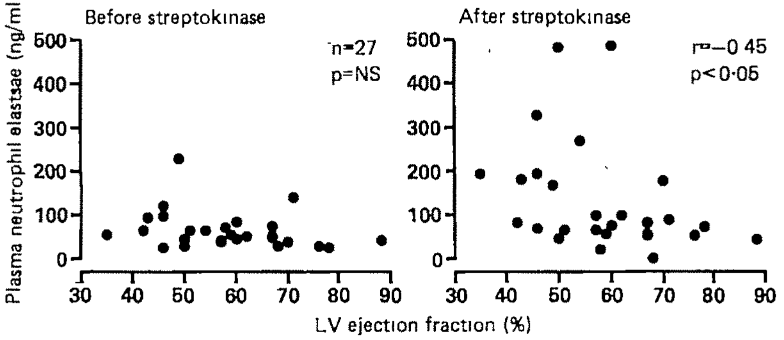


Figure 2 Relation between plasma neutrophil elastase and left ventricular ejection fraction before streptokinase treatment and one hour after it.

cannot distinguish between these separate mechanisms, but experimental data indicate that substantial intramyocardial accumulation of activated neutrophils early after coronary occlusion is not seen in the absence of reperfusion, when an explosive influx occurs.[14,27,28] Moreover, during angioplasty very brief periods of coronary occlusion followed by reperfusion produce a sharp increase in plasma elastase which cannot be explained by washout.[29] Thus washout is unlikely to account for the elastase response seen in the present study and certainly could not account for the increase in circulating neutrophils which was too rapid and too large to have derived from the zone of infarction.

Peripheral leucocytosis in acute myocardial infarction peaks after three to four days and is usually regarded as a component of the generalised stress response.[30] However, this is unlikely to explain the abrupt rise in circulating neutrophils that occurred immediately after thrombolytic treatment in the present study. Streptokinase infusion might itself have contributed to the neutrophil response but cannot have been the major determinant because responses were significantly related to three independent measures of myocardial injury, suggesting that streptokinase induced reperfusion of the ischaemic myocardium caused a reactive leucocytosis in proportion to the degree of injury.

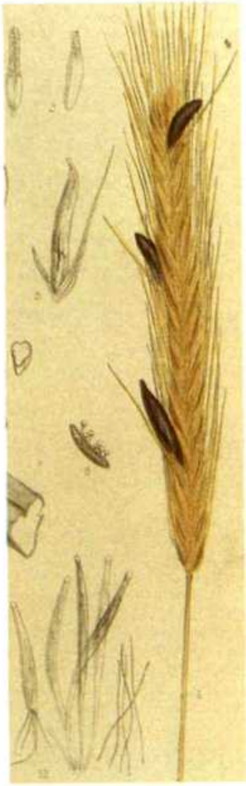
Quantification of myocardial injury and infarct size is difficult and although ejection fraction, peak creatine kinase, and QRS score are widely used,[21,31,32] clinical constraints imposed limitations on our methods. Thus a series of only three blood samples per patient was available for determining the peak creatine kinase activity, and the ejection fraction was measured before hospital discharge in most patients when reversible myocardial stunning may have made a variable contribution to contractile dysfunction.[33] Nevertheless, despite these limitations, relations between neutrophil responses early after thrombolytic treatment and these three independent indices of infarct size showed remarkable consistency, supporting our hypothesis that the neutrophil response provides an early measure of myocardial injury.

We found that thrombolytic treatment in acute myocardial infarction leads to an abrupt increase in circulating neutrophils which provides an early measure of injury. It also leads to neutrophil activation, probably in response to coronary recanalisation and myocardial reperfusion. Activated neutrophils are recognised as mediators of reperfusion injury in experimental infarction and the data in the present study provide preliminary evidence of a similar pathogenic role in the clinical setting.

1 GISSI Effectiveness of intravenous thrombolytic treatment in acute myocardial infarction *Lancet* 1986,i 397–402
2 TIMI Chesebro JH, Knatterud G, Roberts R, *et al* Thrombolysis in myocardial infarction (TIMI) trial, phase 1 a comparison between intravenous tissue plasminogen activator and intravenous streptokinase *Circulation* 1987,76 142–54
3 ISIS-2 Study Group Randomised trial of intravenous streptokinase, oral aspirin, both, or neither among 17,187 cases of suspected acute myocardial infarction ISIS-2 *Lancet* 1988,ii 349–60
4 White HD, Norris RM, Brown MA, *et al* Effect of intravenous streptokinase on left ventricular function and early survival after acute myocardial infarction *N Engl J Med* 1987,317 850–5
5 Scheiber TL, Miller DH, Silvasi DA, Moses JW, Borer JS Randomized double-blind trial of intravenous streptokinase for acute myocardial infarction *Am J Cardiol* 1986,58 47–52
6 Ritchie JL, Davis KB, Williams DL, Caldwell JH, Kennedy JW Global and regional left ventricular function and tomographic radionuclide perfusion the Western Washington intracoronary streptokinase in acute myocardial infarction trial *Circulation* 1984,70 867–75
7 Olson HG, Butman SM, Piters KM, *et al* A randomized controlled trial of intravenous streptokinase in acute myocardial infarction *Am Heart J* 1986,111 1021–9
8 ISAM Study Group Prospective trial of intravenous streptokinase in acute myocardial infarction. mortality, morbidity and infarct size at 21 days *N Engl J Med* 1986;314 1465–71
9 Braunwald E, Kloner RA. Myocardial reperfusion a double edged sword *J Clin Invest* 1985,76 1713–9.
10 Davies SW, Ranjadayalan K, Wickens DG, Dormandy TL, Timmis AD Lipid peroxidation associated with successful thrombolysis *Lancet* 1990,335 741–3
11 Davies SW, Ranjadayalan K, Wickens DG, Dormandy TL, Timmis AD Free radical activity at the time of successful thrombolysis relation to left ventricular function [Abstract] *Br Heart J* 1990,64 83
12 McCord JM Oxygen-derived free radicals in postischemic tissue injury. *N Engl J Med* 1985,312 159–63
13 Mehta JL, Nichols WW, Mehta P Neutrophils as potential participants in acute myocardial ischemia relevance to reperfusion *J Am Coll Cardiol* 1988,11 1309–16
14 Engler RL, Dahlgren MD, Peterson MA, Dobbs A, Schmid-Schoenbein G Accumulation of polymorphonuclear leukocytes during 3 hour experimental myocardial ischemia *Am J Physiol* 1986,251 H93–100
15 O'Flaherty JT, Ward P Chemotactic factors and the neutrophil *Semin Hematol* 1979;16 163–74
16 Mehta J, Mehta P, Lawson DL, Ostrowski N, Brigmon L Influence of a selective thromboxane synthetase blocker CGS-13080 on thromboxane and prostacyclin biosynthesis in whole blood evidence for synthesis of prostacyclin by leukocytes from platelet-derived endoperoxides *J Lab Clin Med* 1985,106 246–52
17 Engler RE Granulocytes and oxidative injury in myocardial ischemia and reperfusion *Fed Proc* 1987,46 2395–6
18 Lucchesi BR Role of neutrophils in ischemic heart disease pathophysiologic role in myocardial ischemia and coronary artery reperfusion In Mehta JL, ed *Thrombosis and platelets in myocardial ischemia* Philadelphia FA Davis, 1987 35–48
19 Hartmann JR, Robinson JA, Gunnar RM Chemotactic activity in the coronary sinus after experimental myocardial infarction effects of pharmacologic interventions on ischemic injury *Am J Cardiol* 1977,40 550–5
20 Romson JL, Hook BG, Kunkel SL, Abrams GD, Schork MA, Lucchesi BR Reduction of the extent of ischemic myocardial injury by neutrophil depletion in the dog *Circulation* 1983,67 1016–23
21 Palmeri ST, Harrison DG, Colele FR, *et al* A QRS scoring system for assessing left ventricular function after myocardial infarction *N Engl J Med* 1982,306 4–9
22 Sandler H, Dodge HT The use of single plane angiocardiograms for the calculation of left ventricular volume in man *Am Heart J* 1968,75 325–34
23 Davies RA, Thakur ML, Berger HJ, Wackers FJ, Gottschalk A, Zaret BL Imaging the inflammatory response to acute myocardial infarction in man using indium-111-labelled autologous leukocytes *Circulation* 1981,63.826–32
24 Bell D, Jackson M, Millar AM, Nicoll JJ, Connell M, Muir AL The acute inflammatory response to myocardial infarction imaging with indium-111 labelled autologous neutrophils *Br Heart J* 1987,57 23–7
25 Bell D, Jackson M, Nicoll JJ, Millar A, Dawes J, Muir AL Inflammatory response, neutrophil activation, and free radical production after acute myocardial infarction effect of thrombolytic treatment *Br Heart J* 1990,63 82–7

26 Gutteridge CN, Burrell C, Newland AC. Neutrophil CR3 expression and leucocyte elastase release during thrombolysis with APSAC. *Br J Haematol* 1988;**69**:116.
27 Mallory GK, White PD, Salcedo-Salger J. The speed of healing of myocardial infarction. *Am Heart J* 1939;**18**:647–71.
28 Sommers HM, Jennings RB. Experimental acute myocardial infarction. *Lab Invest* 1964;**12**:1491–503.
29 De Servi S, Mazzone A, Ricevuti G, *et al.* Granulocyte activation after coronary angioplasty in humans. *Circulation* 1990;**82**:140–6.
30 Pasternak RC, Braunwald E, Sobel BE. Acute myocardial infarction. In: Braunwald E, ed. *Heart disease.* Philadelphia: WB Saunders, 1988:1222–313.
31 Swan HJC, Forrester JS, Diamond G, Chatterjee K, Parmley WW. Hemodynamic spectrum of myocardial infarction and cardiogenic shock. *Circulation* 1972;**45**: 1097–100.
32 Kibe O, Nilsson NJ. Observations on the diagnostic and prognostic value of some enzyme tests in myocardial infarction. *Acta Med Scand* 1967;**182**:597–602.
33 Braunwald E, Kloner RA. The stunned myocardium: prolonged postischemic ventricular dysfunction. *Circulation* 1982;**66**:1146–9.

PLANTS IN CARDIOLOGY



Claviceps purpurea Tul. Bentley R, Trimen H. *Medicinal plants.* vol 4. London: Churchill, 1880: 303. The black bodies are the sclerotia.

Ergometrine (ergonovine)

The fungus *Claviceps purpurea* (Clavicipitaceae) is a parasite that infects the flowers of cereals, notably rye, replacing them with a curved hard mass or sclerotium of mycelia which is called ergot (from Old French argot, a cock's spur). In the Middle Ages rye bread infected with ergot caused large epidemics of gangrene of the hands and feet and mental symptoms. Ergotism was often fatal. The blackened extremities looked as if they had been burnt in a fire, and the malady was called St Anthony's Fire because the patients were treated at the saint's monastery in Padua.

Since 300 BC ergot has been recognised as causing abortion. Thus its vasoconstrictor, oxytocic, and cerebral effects were known long before the responsible alkaloids were isolated. Ergotoxine and ergotamine were the first to be found and their effect on human uterine contraction was studied in 1932 by Chassar Moir. He then tested the traditional liquid extract of ergot which was thought by some scientists, though not by clinicians, to be ineffective and he showed its action to be much larger than the two alkaloids. This led to the isolation of a new alkaloid, ergometrine (ergonovine). Its vasoconstrictor action was first used in the investigation of coronary artery spasm in 1976 by T O Cheng at the suggestion of E Shirey and W Sheldon.

Ergot has been called "a veritable treasure house of pharmacological constituents." Ergot derivatives include the hallucinogen, lysergic acid diethylamide (LSD), bromocriptine (used to treat pituitary tumours and parkinsonism), and the serotonin antagonist, methysergide, which is an effective prophylactic in migraine. Methysergide can cause fibrosis of the mitral and aortic valves.

There are over 200 000 species of fungi. They are of great importance in medicine, producing antibiotics and also cyclosporin. The fungi are by tradition classified as plants but because they differ from them and from animals in several ways there is a proposal to create a separate fungal kingdom.

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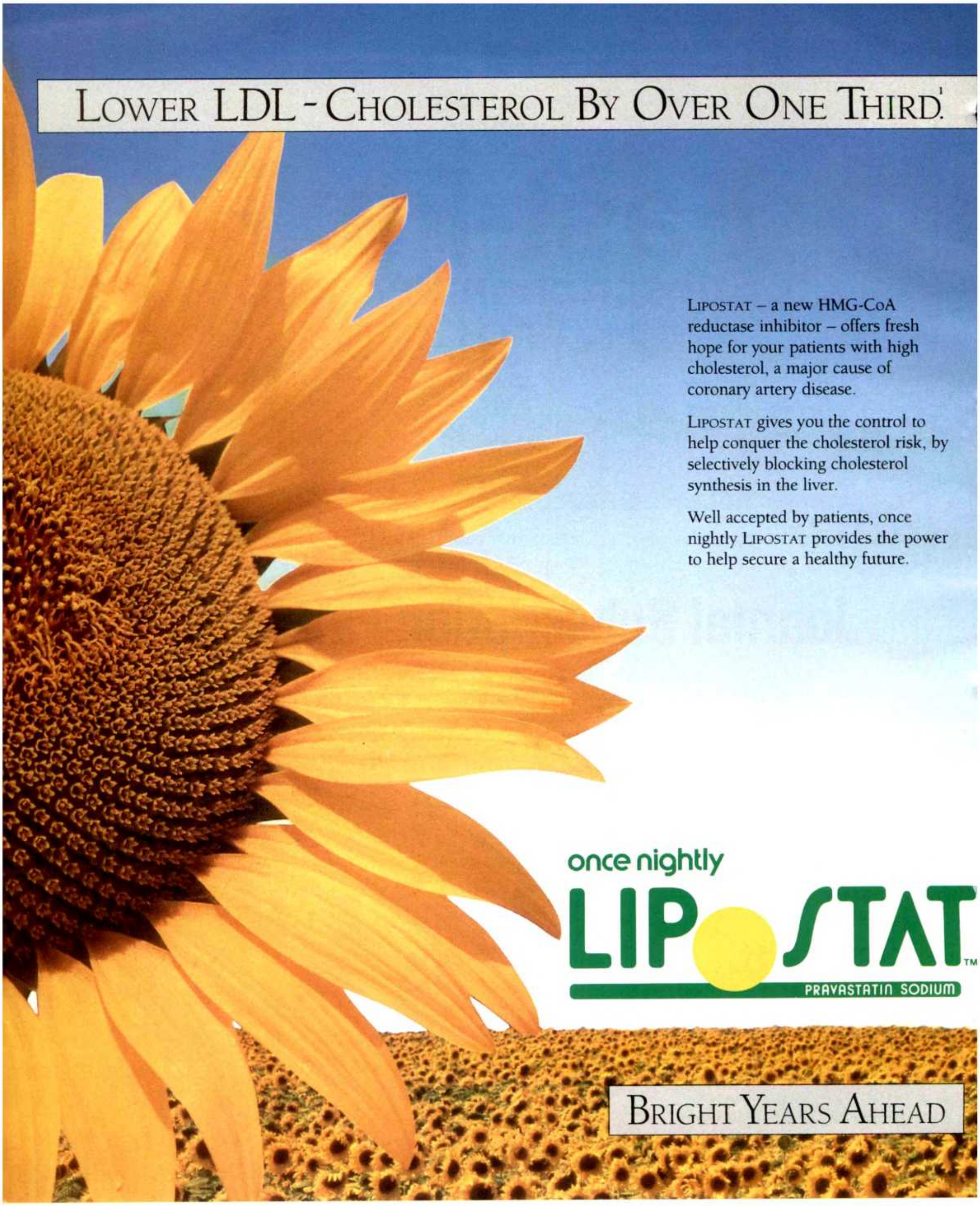

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References

1. Data on file. In trials LIPOSTAT demonstrated an LDL-cholesterol reduction of up to 34% from baseline values (after 8 weeks, 40 mg nightly).

Br Heart J 1991;66.15–8

Aging, autonomic function, and the perception of angina

V Umachandran, K Ranjadayalan, G Ambepitiya, B Marchant, P G Kopelman, A D Timmis

Abstract

***Objective*—To determine the effects of age and autonomic function on the perception of angina.**

***Design*—Prospective evaluation of the relations between anginal perceptual threshold, autonomic function, and systolic blood pressure in patients with symptomatic coronary artery disease. Statistical analysis was by non-parametric techniques.**

***Setting*—Cardiology departments of a district general hospital and a post-graduate teaching centre.**

***Subjects*—82 non-diabetic men with typical exertional angina and coronary artery disease confirmed by arteriography (n = 64) or a history of Q wave infarction (n = 18).**

***Main outcome measures*—Age, anginal perceptual threshold, autonomic function, and blood pressure. Anginal perceptual threshold was defined as the time from onset of 0·1 mV ST depression to the onset of angina during treadmill stress testing. Autonomic function was measured as the ratio of peak heart rate during the Valsalva manoeuvre to the minimum rate after release.**

***Results*—Anginal perceptual threshold showed a weak but significant correlation with age, with older patients tending to have a longer interval between the onset of ST depression and the onset of angina. Comparison of patients in the upper and lower quartile age ranges showed a difference of 50 seconds between median threshold measurements. Blood pressure and heart rate responses to the Valsalva manoeuvre also correlated with age, but neither variable correlated with the anginal perceptual threshold.**

***Conclusions*—In non-diabetic men with coronary artery disease the perception of angina tends to deteriorate with advancing age. The mechanism is unclear but is not attributable solely to alterations in blood pressure or autonomic function.**

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In patients with coronary artery disease angina usually occurs in response to exercise induced myocardial ischaemia. However, there is often a latent interval after the provocation of myocardial ischaemia before chest pain develops. We have called this latent interval the anginal perceptual threshold and have defined it as the time from onset of 0·1 mV ST depression to the onset of angina during treadmill stress testing. Because the anginal perceptual threshold is a continuous variable it provides a useful clinical measure of the perception of angina and may be useful for investigating the mechanisms responsible for silent ischaemia.

Preliminary work has shown that the anginal perceptual threshold is prolonged in diabetes, particularly in patients with autonomic neuropathy,[1] which means that damage to the sensory innervation of the heart may account for the propensity to silent ischaemia in these patients.[2-4] It is not known, however, whether neuropathic mechanisms are active in the silent ischaemia seen in non-diabetic patients with coronary artery disease.[5 6] If neuropathic mechanisms are important in the non-diabetic population, alterations in the perception of angina would be expected to be more common in the elderly because of the tendency for autonomic[7 8] and sensory[9 10] function to deteriorate with increasing age. The Framingham study showed that asymptomatic myocardial infarction is indeed more common in elderly people[11] but information about the effects of aging on the perception of angina is scarce. This information is potentially important not only because the proportion of elderly people is increasing but also because of the insights it might provide into the mechanisms of silent ischaemia. We have measured the anginal perceptual threshold in a group of non-diabetic men with exertional angina to determine the effects of age and autonomic function on the perception of angina.

Patients and methods

PATIENTS

The 82 patients included in this study were non-diabetic men (median age 63 years (range 35–82)). All had typical exertional angina and coronary artery disease confirmed by arteriography (n = 64) or a history of Q wave infarction (n = 18). None had clinical evidence of autonomic or peripheral neuropathy. Patients were required to be in sinus rhythm and were excluded if they had unstable angina, myocardial infarction within the previous three months, or electrocardiographic abnormalities preventing adequate interpretation of the exercise stress test (left bundle branch block, digoxin induced changes in the ST segment or T wave). We also excluded patients with intermittent claudication or musculoskeletal disorders severe enough to interfere with exercise testing. All patients gave written informed consent for participation in this study which had been approved by the Newham Health District Ethical Committee.

TREADMILL STRESS TESTING

The stress tests were all performed by one of three experienced doctors (KR, VU, or GA) and in none of our patients did we rely on clinical observations from paramedical staff. Aspirin and antianginal drugs, except for sublingual glyceryl trinitrate, were stopped at least 12 hours beforehand. Symptom limit exercise testing was carried out on a motor driven treadmill by the Bruce protocol.[12] Patients were exercised for three minute stages at progressively increasing workloads. A 12 lead electrocardiogram was recorded before exercise, at the end of each three minute stage, at peak exercise, and every minute during recovery. Heart rate and blood pressure were recorded at the same intervals. In addition, the three leads previously identified as showing the earliest ST depression were recorded continuously throughout exercise on the electrocardiographic print out in order to identify the time to onset of 0·1 mV ST depression measured 80 ms after the J point. The patients were asked to report the onset of angina and to ensure that the time was accurately identified the doctor inquired about symptoms throughout the test. The anginal perceptual threshold was calculated as the time from the onset of 0·1 mV ST depression to the onset of angina. Three patients who did not experience chest pain during the stress test despite diagnostic ST segment depression were excluded from the analysis of the anginal perceptual threshold.

AUTONOMIC FUNCTION TESTING

This was performed immediately before the treadmill stress test. In every patient heart rate was monitored on the electrocardiogram during and after the Valsalva manoeuvre (40 mm Hg measured against a mercury column). We used the ratio of the peak heart rate during the Valsalva manoeuvre to the minimum rate after release as an index of autonomic function.[13]

Results of treadmill stress tests (median (interquartile range))

Variable	*Result*
Heart rate (beats/min)	
Rest	77 (67–84)
Peak	130 (116–140)
Systolic blood pressure (mm Hg)	
Rest	140 (120–150)
Peak	160 (140–175)
Peak rate-pressure product (mm Hg beats/min × 10^{-3})	20 6 (17 0–23 3)
Sum of ST depression at peak exercise (mV)	0 6 (0 4–0 8)
Time to onset of 0 1 mV ST depression (s)	193 (120–282)
Time to onset of chest pain (s)	228 (147–325)
Anginal perceptual threshold (s)	40 (10–64)

STATISTICAL ANALYSIS

All averaged results were expressed as medians with the interquartile range in parentheses. Non-parametric tests were used for all data comparisons. Correlations between age, blood pressure, autonomic function, and the anginal perceptual threshold were calculated by Spearman's rank method. The Mann-Whitney test was used to compare differences between patients in the upper and lower age quartiles. A two tailed p value of <0·05 was regarded as statistically significant.

Results

ANGINAL PERCEPTUAL THRESHOLD (TABLE)

Treadmill exercise produced physiological increases in blood pressure and heart rate. Every patient developed at least 0 1 mV of planar or down sloping ST segment depression after 193 (120–282) s of exercise with the onset of angina in all but three cases after 228 (147–325) s. In the 79 patients who experienced angina, the anginal perceptual threshold was 40 (10–64) s. The age of these patients ranged from 35 to 82 years and showed a weak but significant correlation with the anginal perceptual threshold ($r = 0·33$, $p < 0·005$), with older patients tending to have a longer latent interval between the onset of ST depression and the onset of angina (fig 1). Thus comparison of the anginal perceptual thresholds in the upper (≥68 years) and lower (≤56 years) quartile age groups confirmed a highly significant difference between the median values (64 (38–98) *v* 14 (-5–51), $p < 0·005$) (fig 2). Neither myocardial ischaemia nor oxygen demand at peak exercise (as judged by the sum of ST depression and the rate-pressure product respectively) correlated with the anginal perceptual threshold.

AUTONOMIC FUNCTION AND BLOOD PRESSURE

Autonomic function, as reflected by heart rate responses to the Valsalva manoeuvre, showed the expected age related changes. Thus in older patients the change in heart rate tended to be less acute during the Valsalva manoeuvre with

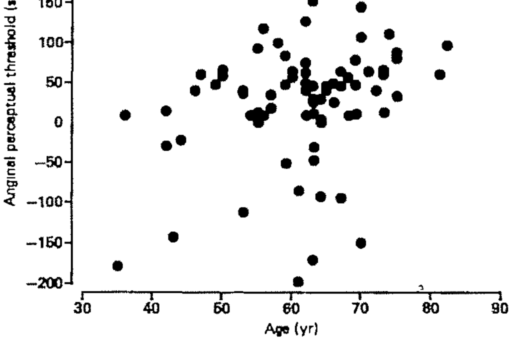
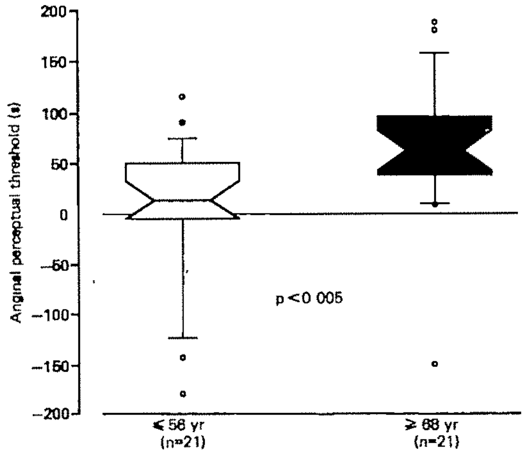


Figure 1 Scattergram (with fitted simple regression) showing relation between age and anginal perceptual threshold. Superimposition of two pairs of data points has reduced by two the number of points visible in the scattergram.

Figure 2 Comparison of anginal perceptual threshold measurements in patients in the upper (≥68 years) and lower (≤56 years) quartile age ranges. Each box plot shows the 10th, 25th, 50th, 75th, and 90th percentile values. The extreme 20% of observed values (10% below the 10th percentile and 10% above the 90th percentile) are shown as open circles. Notches in the box chart represent 95% confidence bands about the median.

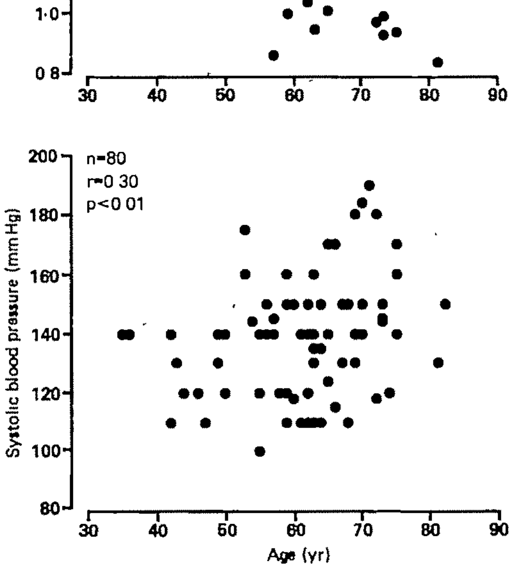


a lower ratio of peak to minimum values (fig 3). Systolic blood pressure also showed the expected correlation with age, older patients tending to have higher systolic measurements (fig 3). Neither autonomic function nor blood pressure, however, showed any relation to the anginal perceptual threshold.

Discussion

This study showed that in non-diabetic men with coronary artery disease the perception of exertional angina shows a weak but significant relation with the age of the patient. With advancing age the latent interval between the onset of regional myocardial ischaemia and the onset of chest pain (the anginal perceptual threshold) becomes longer, such that comparison of patients in the upper and lower quartiles for age range showed a difference of 50 s between median threshold measurements. Although there were the expected relations between age, blood pressure, and heart rate responses to the Valsalva manoeuvre, only age correlated with the anginal perceptual threshold indicating that changes in the perception of angina in the elderly are not attributable solely to alterations in autonomic function.

Figure 3 Scattergrams (with fitted simple regression) showing relations between age, systolic blood pressure, and autonomic function. Superimposition of paired data points (blood pressure 10; Valsalva 1) has caused corresponding reductions in the number of points visible in each scattergram.



The anginal perceptual threshold provides a useful index of the perception of angina in patients with coronary artery disease. Earlier work showed that the threshold can be considerably prolonged in diabetic patients who often do not experience angina until two minutes or longer after the onset of exertional ST depression.[1] Prolongation of the anginal perceptual threshold in diabetes is particularly exaggerated in patients with abnormal autonomic function and is commonly associated with a heightened somatic pain threshold,[14] indicating that the perceptual impairment is generalised and is caused, at least in part, by diabetic neuropathy.[4] The present study indicates that with advancing age a similar, though less pronounced, hyposensitivity to ischaemic cardiac pain develops in non-diabetic patients. The correlation is highly significant but weak, indicating that other factors apart from age are likely to have an independent effect on the perception of angina. Nevertheless, our data suggest that neuropathic mechanisms are less important than in diabetic patients with coronary artery disease.

Recently, Miller *et al* reported age related changes in the perception of angina similar to those in the present study.[15] These changes were independent of the severity of ischaemia, which supports our own findings that myocardial ischaemia and oxygen demand at peak exercise (as judged by the sum of ST depression and the rate-pressure product, respectively) were unrelated to the anginal perceptual threshold. Miller *et al* suggested that the dysfunctional perception might reflect the tendency for blood pressure to rise with age; this suggestion was based on previous reports of increased pain thresholds in hypertensive patients.[16 17] It accorded with the work of Sheps *et al* who described a relation between systolic blood pressure and silent ischaemia in patients with angina and identified a potential role for altered baroreceptor function.[18]

The sensory supply to the heart is part of the autonomic innervation and changes in autonomic function and blood pressure certainly provide a plausible explanation for the age-related increase in the anginal perceptual threshold shown in the present study. However, although our data showed the expected changes in autonomic function and blood pressure in the older age group, neither of these variables was related to the anginal perceptual threshold; this indicated that other mechanisms must contribute to the impairment of perception with increasing age. A generalised hyposensitivity to pain has been seen in the elderly[9 10] and it has been suggested that this might be the result of central modulation by endogenous opioid peptides,[19] though whether this accounts for the prolongation of the anginal perceptual threshold with advancing age remains speculative. Indeed, the mechanism of hypoalgesia in the elderly is at present uncertain but is likely to be multifactorial involving functional alterations in the peripheral and central nervous systems.

The increase in the anginal perceptual threshold with advancing age seems less pronounced than in diabetic patients who can develop profound exertional ischaemia before they experience angina.[20] Nevertheless, any delay in the perception of angina during exertional ischaemia will increase the ischaemic burden in the elderly which may in turn heighten the risk of cardiac arrhythmias and ongoing myofibrillar damage. A similar risk has been ascribed to patients with silent ischaemia and clearly there may be some heterogeneity between silent ischaemia and prolongation of the anginal perceptual threshold.[21] It is not known, however, whether the tendency for the anginal perceptual threshold to increase in elderly patients with coronary artery disease is associated with an increase in the prevalence of silent ischaemia and more work is necessary to define the relation between these perceptual disorders and to determine their clinical significance.

1 Ambepitiya G, Kopelman PG, Ingram D, Swash M, Mills PG, Timmis AD Exertional myocardial ischemia in diabetes· a quantitative analysis of anginal perceptual threshold and the influence of autonomic function. *J Am Coll Cardiol* 1990;15·72–7.

2 Chiariello M, Indolfi C, Cotecchia MR, Sifola C, Romano M, Condorelli M. Asymptomatic transient ST changes during ambulatory ECG monitoring in diabetic patients. *Am Heart J* 1985,110:529–34.

3 Nesto RW, Phillips RT, Kett KG, *et al.* Angina and exertional myocardial ischemia in diabetic and non-diabetic patients. assessment by exercise thallium scintigraphy *Ann Intern Med* 1988;108 170–5.

4 Murray DP, O'Brien T, Mulrooney R, O'Sullivan DJ. Autonomic dysfunction and silent myocardial ischaemia on exercise testing in diabetes mellitus *Diabetic Med* 1990;7.580–4.

5 Fox KM Silent ischaemia clinical implications in 1988 *Br Heart J* 1988,60:363–6

6 Sheps DS, Maixner W, Hinderliter AL. Mechanisms of pain perception in silent myocardial ischemia. *Am Heart J* 1990,119 983–7.

7 Collins KJ, Exton-Sith AK, James MH, Oliver DJ. Functional changes in autonomic responses with ageing. *Age Ageing* 1980;9 17–24

8 O'Brien IAD, O'Hare P, Corrall RJM Heart rate variability in healthy subjects effect of age and the derivation of normal ranges for tests of autonomic function *Br Heart J* 1986;55 348–54.

9 Harkins SW, Price DP, Martelli M Effects of age on pain perception thermonociception. *J Gerentol* 1986;41.58–63.

10 Neri M, Agazzani E. Aging and right-left asymmetry in experimental pain measurement. *Pain* 1984;19:43–8

11 Kannel WB, Abbott RD. Incidence and prognosis of unrecognized myocardial infarction an update on the Framingham study. *N Engl J Med* 1984,311 1144–7

12 Bruce RA. Exercise testing of patients with coronary heart disease *Ann Clin Res* 1971,3·323–32.

13 Ewing DJ, Clarke BF. Diagnosis and management of diabetic autonomic neuropathy *BMJ* 1982;285·916–9.

14 Umachandran V, Ranjadayalan K, Ambepitiya G, Marchant B, Kopelman PG, Timmis AD The perception of angina in diabetes: relation to somatic pain threshold and autonomic function. *Am Heart J* (in press).

15 Miller PF, Sheps DS, Bragdon EE, *et al.* Aging and pain perception in ischemic disease. *Am Heart J* 1990,120 22–30.

16 Dworkin BR, Filewich RJ, Miller NE, Craigmyle N, Pickering TG. Baroreceptor activation reduces reactivity to noxious stimulation implications for hypertension. *Science* 1979;205 1299–301

17 Ghione S, Rosa C, Mezzasalma L, Panattoni E. Arterial hypertension is associated with hyperalgesia in humans *Hypertension* 1988,12·491–7.

18 Sheps DS, Maixner W, Hinderliter AL, *et al.* The relationship between systolic blood pressure, ventricular volume and ischemic pain perception in patients with angina pectoris a potential role for baroreceptors *Isr J Med Sci* 1989;25 482–7

19 Saavendra JM. Naloxone reversible decrease in pain sensitivity in young and adult spontaneously hypertensive rats. *Brain Res* 1987;209.245–9

20 Ranjadayalan K, Umachandran V, Ambepitiya G, Kopelman PG, Mills PG, Timmis AD. Prolonged anginal perceptual threshold in diabetes effects on exercise capacity and myocardial ischemia. *J Am Coll Cardiol* 1990;16 1120–4.

21 Cohn PF Silent myocardial ischemia in patients with a defective anginal warning system. *Am J Cardiol* 1980; 45 697–702.

Br Heart J 1991;66:19–21

Angiotensin converting enzyme inhibitors and magnesium conservation in patients with congestive cardiac failure

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Abstract

***Objective*—To investigate whether angiotensin converting enzyme inhibitors reduce diuretic induced magnesium excretion in patients in congestive cardiac failure.**

***Design*—Cohort analytic study.**

***Setting*—A London district general hospital.**

***Subjects*—Thirty four patients with chronic congestive cardiac failure caused by ischaemic heart disease or cardiomyopathy selected consecutively from inpatients under the care of two consultant cardiologists. Nineteen patients (group 1) on diuretics alone were compared with 15 patients (group 2) taking diuretics plus either enalapril or captopril. All drug regimens were stable for at least three months before the study. Patients with impaired renal function (plasma creatinine >120 μmol/l) were excluded.**

***Interventions*—An intravenous loading dose of magnesium sulphate was given to minimise the variability in baseline magnesium state.**

***Main outcome measure*—Total urine magnesium excretion and creatinine clearance in 24 hour urine collections.**

***Results*—Plasma magnesium was similar in the two groups. However, 24 hour urine magnesium excretion was significantly lower in group 2 than in group 1. Furthermore, creatinine clearance was also significantly lower in group 2 and correlated strongly with magnesium excretion. There was no such relation in group 1. There was no difference in fractional clearance of magnesium between groups.**

***Conclusion*—Angiotensin converting enzyme inhibitors have an important magnesium conserving action, possibly via their effect on glomerular filtration rate.**

There is growing awareness of the importance of magensium metabolism in cardiovascular medicine and in particular the association between hypomagnesaemia and cardiac arrhythmias.[1] Recent evidence suggests that hypomagnesaemia in patients with congestive cardiac failure is related to a poor prognosis owing to a high prevalence of ventricular arrhythmias and to an increased risk of sudden death.[2] Interestingly, hypermagnesaemia in these patients may also be associated with an adverse prognosis, though raised plasma concentrations of magnesium may simply be a marker of important renal impairment caused by severe cardiac dysfunction.

Angiotensin converting enzyme inhibitors are commonly used with loop diuretics to treat congestive cardiac failure. It is well recognised that loop diuretics can cause hypomagnesaemia,[3] and furthermore, that plasma magnesium concentrations can be normal in the presence of significant tissue depletion.[4] Angiotensin converting enzyme inhibitors may attenuate the hypomagnesaemic action of loop diuretics[5]; their effect on urinary magnesium excretion has not been adequately studied. We investigated the effects of angiotensin converting enzyme inhibitors on diuretic induced magnesium excretion in patients with congestive cardiac failure.

Patients and methods

We studied 34 patients with chronic congestive cardiac failure caused by ischaemic heart disease or cardiomyopathy. Group 1 (n = 19) patients were treated with a loop diuretic (either frusemide with or without amiloride or bumetanide) alone. Patients in group 2 (n = 15) were taking both a loop diuretic plus an angiotensin converting enzyme inhibitor (enalapril or captopril). All drug regimens were kept stable for at least three months before the study. Patients with impaired renal function (plasma creatinine >120 μmol/l) were excluded. Other exclusion criteria included factors likely to disturb renal magnesium homoeostasis such as alcoholism, malabsorption, and ingestion of compounds containing magnesium. Blood was taken for baseline plasma magnesium and creatinine estimations. To minimise the variability in the

Table 1 Age, weight (kg), and dose of diuretic (equivalent to dose of frusemide in mg) in the two patient groups (mean (SEM))

	Group 1 (Diuretics only)	*Group 2 (Diuretics + ACE inhibitors)*
Age	69 (2 5)	69 (2 6)
Weight (kg)	70 (2 7)	71 (3 8)
Diuretic dose	80 (8 4)	91 (9 9)
Dose ACE inhibitor (=mg enalapril)	—	15 (2 6)

Table 2 Plasma magnesium (mmol/l) and 24 h urinary magnesium (mmol) in the two groups (mean (SEM)

	Group 1 (Diuretics only)	*Group 2 (Diuretics and ACE inhibitors)*	*p Value*
Plasma magnesium (mmol/l)	0 87 (0 02)	0 86 (0 02)	NS
24 h urine magnesium (mmol/24 h)	26 0 (1 0)	18 5 (1 4)	0 001

baseline state of total body magnesium all patients were given an intravenous loading dose of magnesium sulphate (30 mmol in 500 ml of 5% dextrose given over eight hours). This loading regimen has been used in previous studies of magnesium turnover.[6] We measured total urinary magnesium and creatinine in urine collected for 24 hours.

The statistical significance of differences between the two groups was assessed by the two tailed *t* test for groups of non-paired observations. Linear regression analysis was applied to test for a relation between sets of variables within a group.

Results

Patients in the two groups were well matched for age, weight, and dose of diuretic (table 1). Table 2 shows the mean (SEM) values of plasma magnesium and 24 hour urinary magnesium in the two groups of patients. Plasma magnesium concentrations were similar in both groups and were within the normal range. However, the 24 hour excretion of magnesium was significantly lower in the patients (group 2) treated with angiotensin converting enzyme inhibitor. Table 3 shows the mean (SEM) values of plasma creatinine, creatinine clearance, and fractional clearance of magnesium. Although plasma creatine concentrations were comparable, creatinine clearance was significantly lower in group 2. There was no significant difference in the fractional clearance of magnesium between the groups.

Linear regression analysis showed a strong relation ($p = 0{\cdot}001$) between urine magnesium excretion and creatinine clearance in patients treated with angiotensin converting enzyme inhibitors (figure). There was no such relation in the patients who were not treated with angiotensin converting enzyme inhibitors (group 1).

Discussion

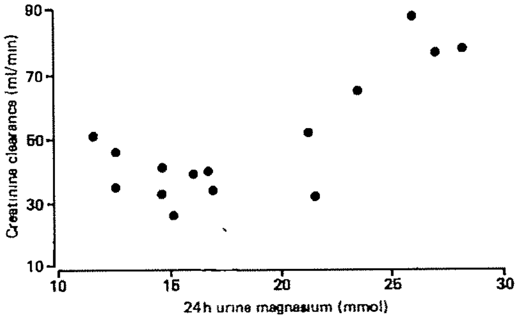
Our results suggest that angiotensin converting enzyme inhibitors have a magnesium conserving effect when they are given in conjunction with loop diuretics to treat congestive cardiac failure. As far as we are aware this effect has not been shown before. Previous studies of angiotensin converting enzyme inhibitors and magnesium turnover have been restricted to plasma concentrations, and the results have been conflicting.[5 7 8] In this study, plasma magnesium concentrations were within the normal range with no significant difference between the two groups. It might be expected that the group treated with diuretics alone would have a lower plasma magnesium concentration than the group receiving diuretics and angiotensin converting enzyme inhibitors. However, other workers showed that plasma magnesium concentrations do not correlate with tissue concentrations,[4 9] and thus plasma concentrations within the normal range do not exclude significant tissue or total body depletion. To establish whether tissue magnesium concentrations differed between the two groups, and in particular whether patients in group 1 were tissue depleted, would have required analysis of muscle biopsy specimens.

Table 3 Plasma creatinine (μmol/l), creatinine clearance (ml/min), and fractional clearance of magnesium (%) in the two groups (mean (SEM)

	Group 1 (Diuretics only)	*Group 2 (Diuretics and ACE inhibitors)*	*p Value*
Plasma creatinine (μmol/l)	98 (5·5)	112 (5 3)	NS
Creatinine clearance (ml/min)	74 (5 9)	49 (5 0)	0 002
Fractional magnesium clearance (%)	29 5 (2 1)	32 6 (2 4)	NS

About 80% of plasma magnesium is filtered at the glomerulus and most is reabsorbed in the ascending loop of Henle.[10] Loop diuretics increase urinary magnesium losses largely by blocking reabsorption at this site, though secondary hyperaldosteronism may be a contributory factor.[10 11]

In this study patients in group 2 had a significantly lower glomerular filtration rate, which we propose was directly related to angiotensin converting enzyme inhibition. Furthermore, the strong correlation between urinary magnesium excretion and creatinine clearance in group 2 suggests that magnesium conservation may largely be a result of the reduction in glomerular filtration rate. The absence of such a correlation in group 1 may mean that magnesium excretion only becomes dependent on glomerular filtration rate when this is reduced below a critical value. Fractional clearance of magnesium was similar between the two groups, suggesting that angiotensin enzyme inhibitors do not have a significant effect on magnesium reabsorption at a site other than the glomerulus. Nevertheless, it is also possible that the anti-aldosterone action of angiotensin converting enzyme inhibitors may



Relation between creatinine clearance and 24 h urine magnesium in patients on diuretics and angiotensin converting enzyme inhibitors.

contribute to magnesium conservation, though for confirmation this needs further investigation. An alternative explanation for our findings is that by chance the angiotensin converting enzyme inhibitor group had worse renal function and the differences shown were attributable to this and not to the drugs themselves. However, we think that this is an unlikely explanation.

First, we were careful to exclude from this study patients likely to have intrinsic renal disease. Secondly enalapril (and presumably other angotensin converting enzyme inhibitors) has been shown to reduce the glomerular filtration rate measured both by isotope techniques and by creatinine clearance.[5] There is increasing evidence that in severe cardiac failure the glomerular filtration rate is maintained by angiotensin mediated vasoconstriction of the efferent glomerular arteriole. By inhibiting this mechanism, angotensin converting enzyme inhibitors reduce the glomerular hydrostatic pressure and hence the glomerular filtration rate.[12]

The only important difference between the two groups in terms of concurrent medication was that more patients in group 1 were receiving amiloride (15 in group 1 and four in group 2). This is unlikely to have adversely influenced our results because amiloride can have only a weak magnesium conserving action,[13] and so would tend to lessen the difference seen between the groups. The only other commonly prescribed drugs were long acting nitrates and digoxin, both of which were evenly distributed between groups.

The high incidence of sudden death among patients in cardiac failure implies that lethal ventricular arrhythmias are in part responsible. Hypomagnesaemia has been associated with ventricular extrasystoles and this may partly explain the high incidence of ventricular arrhythmias in patients in congestive cardiac failure.[14]

We suggest that angiotensin converting enzyme inhibitors have an important magnesium sparing action in patients whom are liable to depletion by loop diuretics.

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1 Whang R Magnesium deficiency· pathogenesis, prevalence and clinical implications *Am J Med* 1987,**82**(suppl 3A) 24–9

2 Gottlieb SS, Baruch L, Kukin ML, *et al* Prognostic importance of the serum magnesium concentration in patients with congestive heart failure *J Am Coll Cardiol* 1990,**16** 827–31

3 Ryan MP Diuretics and potassium/magnesium depletion *Am J Med* 1987,**82** (suppl 3A) 38–42

4 Dorup I, Skajaa K, Clausen T, Kjeldsen K Reduced concentrations of potassium, magnesium, and sodium-potassium pumps in human skeletal muscle during treatment with diuretics. *BMJ* 1988,**296**.455–8

5 Cleland JGF, Dargie HJ, Ball SG, *et al*. Effects of enalapril in heart failure a double blind study of effects on exercise performance, renal function, hormones, and metabolic state *Br Heart J* 1985,**54** 305–12

6 Dyckner T, Wester PO Magnesium deficiency guidelines for diagnosis and substitution therapy. *Acta Med Scand* 1982,**661**(suppl) 37–41

7 Zumkley VH, Bertram HP, Vetter H, *et al* Magnesium and zinc concentrations in plasma and erythrocytes under angiotensin converting enzyme inhibition *Magnesium Bull* 1983;**2** 74–7

8 Vandenburg MJ, Robinson P, Arr S, Cooper W, Currie WJC Serum magnesium is unaffected by angiotensin converting enzyme inhibition *Clin Sci* 1985;**68**(suppl 11) 77p–8p

9 Dyckner T, Wester PO Potassium/magnesium depletion in patients with cardiovascular disease *Am J Med* 1987, **82** (suppl 3A) 11–6

10 Dirks JH The kidney and magnesium regulation *Kidney Int* 1983,**23** 771–7

11 Rasmussen H, McNair P, Goransson L, *et al* Magnesium deficiency in patients with ischaemic heart disease with and without acute myocardial infarction uncovered by an intravenous loading dose *Arch Intern Med* 1988,**148** 329–32

12 Packer M, Lee WH, Kessler PD Preservation of glomerular filtration rate in human heart failure by activation of the renin-angiotensin system. *Circulation* 1986,**74** 766–4

13 Leary WP, Reyes AJ, van de Byl K Effect of a combination of hydrochlorothiazide and amiloride on urinary magnesium excretion in healthy adults *Curr Ther Res* 1984,**35**. 293–300

14 Hollifield JW Magnesium depletion, diuretics, and arrythmias. *Am J Med* 1987,**82**(suppl 3A) 30–7

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Intracardiac mobile thrombus and D-dimer fragment of fibrin in patients with mitral stenosis

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Abstract

***Objective*—To investigate the relation between intracardiac thrombus and blood coagulability in patients with mitral stenosis.**

***Design*—Prospective study. Cross sectional echocardiography and plasma concentrations of the D-dimer fragment of fibrin were used concurrently to detect intracardiac thrombus in patients with mitral stenosis.**

***Setting*—Department of Medicine, National Cardiovascular Centre, Osaka, Japan.**

***Patients*—63 patients with mitral stenosis. None of them had been receiving any anticoagulants or antiplatelet agents.**

***Main outcome measures*—Plasma concentrations of D-dimer in patients with a mobile intracardiac thrombus, those in patients with a non-mobile intracardiac thrombus, and those in patients without an intracardiac thrombus.**

***Results*—A mobile intracardiac thrombus was found in 10 patients and a non-mobile thrombus in eight. The remaining 45 patients had no intracardiac thrombi. Plasma concentrations of D-dimer in the 10 patients with a mobile thrombus were all >300 ng/ml (mean 983·3, 95% confidence interval 498·9 to 1467·7 ng/ml) and they were significantly higher than those in the patients with a non-mobile thrombus (226·2, 33·6 to 418·8 ng/ml) and the patients without an intracardiac thrombus (147·2, 110·4 to 184 ng/ml).**

***Conclusions*—A high plasma concentration of D-dimer seemed to reflect a hypercoagulable intracardiac state and may be a helpful indicator of the possible presence of mobile intracardiac thrombus in patients with mitral stenosis.**

Plasma concentrations of the D-dimer fragment of fibrin and fibrinopeptide A have been measured to assess hypercoagulability and the secondary enhancement of fibrinolysis in patients with various disorders of the circulatory system.[1-3] However, the relation between intracardiac thrombus and blood coagulability has not been fully elucidated in patients with mitral stenosis.

To investigate this relation we used cross sectional echocardiography and we measured the plasma concentrations of D-dimer and other indices of blood coagulation concurrently in 63 patients with mitral stenosis.

Patients and methods

STUDY POPULATION

We studied 63 patients with mitral stenosis aged 53·7 (10·8) years (mean (SD)), all of whom were inpatients or outpatients at the National Cardiovascular Centre between 1 December 1987 and 31 October 1988, and 10 healthy volunteers aged 54·3 (11·9) years. None of the patients with mitral stenosis had been taking anticoagulants, antiplatelet agents, or any other drugs that influence the haematological indices. They were all free from moderate or severe mitral regurgitation as determined by colour Doppler echocardiography.[4]

CROSS SECTIONAL ECHOCARDIOGRAPHY

For echocardiography we used a commercially available real time, phased array system (Toshiba SSH-60A) with a 3·75 MHz transducer. Subjects were examined in the left lateral or supine position. The heart chambers, especially the left atrial cavity, were examined extensively by shifting, rotating, and tilting the transducer and by adjusting the gain control of the equipment whenever necessary. The criteria for the echocardiographic diagnosis of intracardiac thrombi have been reported elsewhere.[5] A thrombus was diagnosed when an echogenic mass with a clearly defined contour was seen inside the cardiac cavity, when the endocardial surface echo of the cardiac wall could be identified, and when the mass was visualised from various positions on the chest wall. The thrombus was regarded as mobile if a portion of the thrombus showed motion independent from that of the adjacent endocardium, which was either opposite in direction or freely erratic. The left atrial dimensions were measured at the same time.[6]

COAGULATION STUDIES

On the same day as cross sectional echocardiography we performed the following coagulation studies: haematocrit; plasma concentrations of fibrinopeptide A, fibrinopeptide Bβ15–42, D-dimer, antithrombin III; and the prothrombin time and activated partial thromboplastin time. Plasma concentrations of fibrinopeptide A, fibrinopeptide Bβ15–42, and D-dimer were measured as follows.

After discarding the first 2 ml of blood we drew 1·6 ml from the antecubital vein into a precooled silicone coated tube containing 1·0 ml of inhibitor (aprotinin 10 000 U/ml and heparin 500 U/ml). The tube was immediately inverted gently several times and then centrifuged at 2000 *g* (3000 rpm) for 15 minutes at 4°C. The supernatant was then placed in plastic tubes and stored frozen at −20°C. Plasma concentrations of fibrinopeptide A were determined by enzyme immunoassay (Asserachrom FPA, Diagnostica Stago, Francoville, France) and those of fibrinopeptide Bβ15–42 by radioimmunoassay (Fibrinopeptide Bβ15–42 radioimmunoassay, IMCO Corporation, Stockholm, Sweden).[7] D-dimer concentrations were measured by enzyme immunoassay (Dimertest EIA, Agen Biomedical, Brisbane, Australia).[8] The prothrombin time was assessed by Quick's one-stage prothrombin time method by Thromborel S (Behringwerke, Marburg, Germany) and was expressed as the international normalised ratio.[9] Antithrombin III concentrations were measured by the chromogenic substrate method (Substrate: S-2238, KabiVitrum AB, Sweden).[10] The observers of the cross sectional echocardiographic studies were blinded to the results of these haematological investigations.

HISTORY OF EMBOLIC EVENTS

We reviewed the history of all patients for any unequivocally documented episodes of arterial embolisation that were confirmed by angiography (cerebral and peripheral vessels), scintigraphy (kidneys), or computed tomography (brain), in addition to a history of the typical clinical signs of embolism.[11]

STATISTICAL ANALYSIS

Continuous data were expressed as the mean (SE). Groups were compared by analysis of variance followed by Duncan's intergroup comparison test; the χ^2 test was also used.

Results

CROSS SECTIONAL ECHOCARDIOGRAPHY

Intracardiac thrombi were shown by echocardiography in 18 of the 63 patients (group 1). Ten of these 18 patients had mobile thrombi (**fig** 1), nine of which were at the left atrial appendage and the other of which was on the left atrial posterior wall. The remaining eight thrombi were non-mobile (fig 2), with seven being at the left atrial appendage and the other one being on the left atrial posterior wall. In the remaining 45 patients, there were no intracardiac thrombi (group 2).

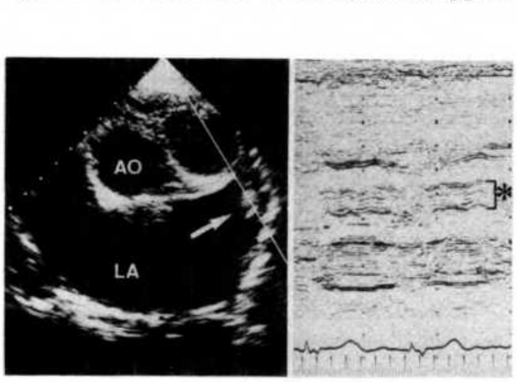

*Figure 1 Left parasternal short axis view (cross sectional and M mode echocardiograms) from a patient with mitral stenosis. Thrombus (arrow and *) at the left atrial appendage was mobile. AO, aorta; LA, left atrium.*

The left atrial dimensions of the 10 healthy volunteers and groups 1 and 2 were 27·0 (1·1 mm), 54·6 (1·5) mm, and 52·8 (1·2) mm, respectively. The left atrial dimensions of groups 1 and 2 were significantly larger than those of the controls ($p < 0·01$), but there was no significant difference between the two groups with mitral stenosis.

Forty four of the 63 patients had atrial fibrillation: 28 (62·2%) without intracardiac thrombi and 16 (88·9%) in those with intracardiac thrombi. There was no significant difference in the incidence of fibrillation between the two groups (χ^2 test).

COAGULATION STUDIES

Plasma concentrations of fibrinopeptide A, fibrinopeptide Bβ15–42, and D-dimer were significantly higher and those of antithrombin III were significantly lower in groups 1 and 2 than in the controls (table). Moreover, the plasma concentrations of fibrinopeptide A and D-dimer in group 1 were significantly higher than those in group 2. There were no significant differences in the haematocrit, prothrombin time, and activated partial thromboplastin time among groups 1 and 2 and the controls.

The plasma concentrations of D-dimer in the patients with mobile thrombi were all above 300 ng/ml (983·3 (242·2) ng/ml) and they were significantly higher than those in the patients with non-mobile thrombi (226·4 (96·3) ng/ml, $p < 0·05$) (fig 3). There were no significant differences other than the D-dimer concentration between the patients with and without mobile thrombi.

HISTORY OF EMBOLIC EVENTS

Of the 63 patients, 22 had a history of confirmed arterial embolism to the brain, kidney (n = 2), or limbs (n = 2) (including four patients with more than one event). All 22 patients had suffered these embolic events more than one month before this study. Nine of the 22 patients

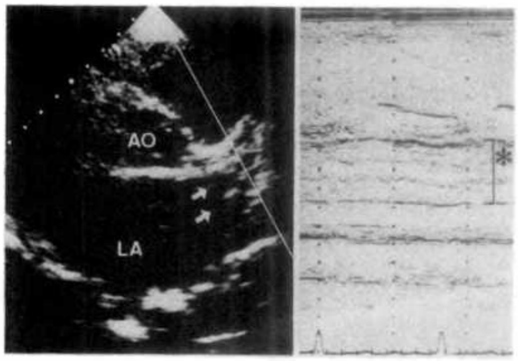

*Figure 2 Left parasternal short axis view (cross sectional and M mode echocardiograms) from a patient with mitral stenosis. Thrombus (arrows and *) at the left atrial appendage was not mobile. AO, aorta; LA, left atrium.*

Haemostatic markers in patients with mitral stenosis with thrombi and without and in controls

		Patients with mitral stenosis	
	Controls (n = 10)	*Without thrombi (n = 45)*	*With thrombi (n = 18)*
Fibrinopeptide A (ng/ml)	0·9 (0·2)	22·9 (6·0)*	50·7 (13·0)*†
Fibrinopeptide Bβ15–42 (ng/ml)	2·7 (0·3)	7·8 (1·5)*	11·9 (1·8)*
D-dimer (ng/ml)	88·5 (10·9)	147·2 (18·4)*	646·9 (165·2)*‡
Antithrombin III (%)	102·5 (2·1)	91·0 (2·1)*	84·5 (3·7)*
Haematocrit (%)	43·5 (0·9)	41·4 (3·8)	42·8 (3·5)
Prothrombin time (INR)	0·99 (0·2)	1·02 (0·02)	1·00 (0·01)
Activated partial thromboplastin time (s)	30·0 (0·9)	32·0 (0·5)	30·6 (0·6)

*$p < 0.01$ *v* controls, †$p < 0.05$ *v* patients without thrombi, ‡$p < 0.01$ *v* patients without thrombi.
INR, International Normalised Ratio.

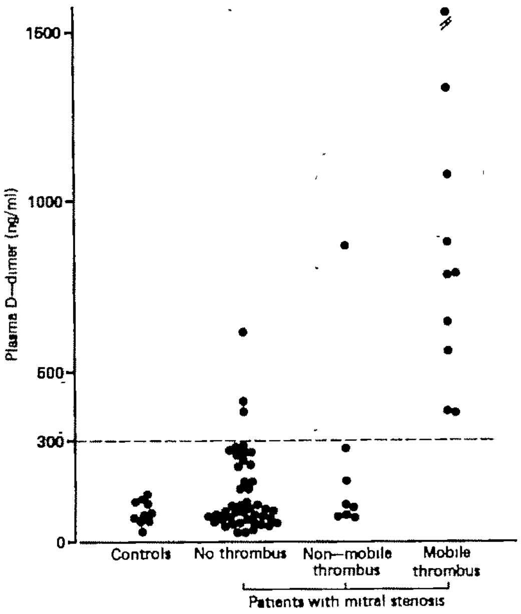

Figure 3 Plasma concentrations of D-dimer in patients with mitral stenosis with thrombi and without. Patients with a thrombus were divided into two subgroups: those with a mobile thrombus and those with a non-mobile thrombus.

had a mobile thrombus and the other 13 did not. The remaining 41 of the 63 patients had not had either cerebral embolism or embolisation to other parts of the body.

None of the 63 patients had other diseases, such as deep vein thrombosis, renal disease, or liver disease, that could have influenced the results of the haematological investigations.

Discussion

Systemic arterial embolism is a common and important complication of mitral stenosis.[12 13] Intracardiac thrombus is very important as a direct source of systemic embolism. Atrial fibrillation and an increase in left atrial dimensions both predispose to the development of intracardiac thrombi.[12 14] In our study, there were no significant differences in the incidence of atrial fibrillation or in the left atrial dimensions between groups 1 and 2. Thus these factors are not invariably associated with intracardiac thrombi.

The plasma concentrations of fibrinopeptide A, fibrinopeptide Bβ15–42, and D-dimer were significantly higher in the patients with mitral stenosis. Plasma concentrations of antithrombin III, however, were significantly lower in groups 1 and 2 than in the controls. These findings are consistent with a previous report that blood coagulability is enhanced in patients with mitral stenosis.[15] Plasma concentrations of fibrinopeptide A, fibrinopeptide Bβ15–42, and D-dimer were also higher in the patients with intracardiac thrombi than in those without. The deposition of fibrin on to an intravascular thrombus is a function of the surface area of the clot and also of the activity of the thrombotic factors associated with the clot. Hence, even small clots can result in active fibrin deposition and the production of D-dimer, fibrinopeptide A, and fibrinopeptide Bβ15–42.

Because blood samples were taken from an antecubital vein our result could have been influenced by thrombosis elsewhere or by emboli from the intracardiac source. However, no patients had a thrombotic disease other than the intracardiac thrombus or a past history of embolism. In all patients with a history of embolism, the interval between the onset of embolism and the study was more than a month, which is sufficient time for the emboli to have resolved spontaneously.[16] Thus we do not believe that such factors are likely to have influenced the results.

D-dimer concentrations in the patients with intracardiac mobile thrombi were all above 300 ng/ml, while those in most patients with non-mobile thrombi or without thrombi were below 300 ng/ml. These data suggest that there was more activation of blood coagulability in the patients with mobile thrombi than in those with non-mobile thrombi, so mobile clots may be associated with more active fibrin deposition than non-mobile clots. However, four patients with non-mobile thrombi or no thrombi had D-dimer concentrations greater than 300 ng/ml. It is possible that they may have had a mobile thrombus in the left atrium that was smaller than the resolution of our echocardiograph, or a mobile thrombus at the tip of the left atrial appendage which is difficult to see from the transthoracic approach.

In a previous study, we reported on 30 consecutive patients with acute cardiogenic cerebral embolism who were examined by serial cross sectional echocardiography.[17] In three of the patients who had mitral stenosis and a newly formed mobile thrombus at the left atrial appendage systemic embolism recurred. In the current study, nine of the 10 patients with mobile thrombus had a past history of embolism whereas none of the eight patients with non-mobile thrombus had such a history. Thus a mobile thrombus seems to be fresher and more liable to be released from the cardiac wall to cause systemic emboli. It also seems to be more likely to regrow.

In conclusion, high plasma concentrations of D-dimer are believed to reflect an intracardiac hypercoagulable state, and measurement of the D-dimer concentration may be useful as a screening method for an increased risk of intracardiac mobile thrombi in patients with mitral stenosis.

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1 Nossel HL, Ti M, Kaplan KL, Spanondis K, Soland T, Butler VP The generation of fibrinopeptide A in clinical blood samples. *J Clin Invest* 1976,58 1136–44.

2 Theroux P, Latour JG, Léger-Gauthier C, Lara JD. Fibrinopeptide A and platelet factor levels in unstable angina pectoris *Circulation* 1987,75 156–62

3 Declerck PJ, Mombaerts P, Holvoet P, De Mol M, Collen D Fibrinolytic response and fibrin fragment D-dimer levels in patients with deep vein thrombosis *Thromb Haemost* 1987,58.1024–9

4 Miyatake T, Izumi S, Okamoto M, *et al.* Semiquantitative grading of severity of mitral regurgitation by real-time two-dimensional Doppler flow imaging technique *J Am Coll Cardiol* 1986,7 82–8

5 Beppu S, Park YD, Sakakibara H, Nagata S, Nimura Y Clinical features of intracardiac thrombosis based on echocardiographic observation *Jpn Circ J* 1984,48 75–82

6 Shan DJ, DeMaria A, Kisslo J, Weyman A Recommendations regarding quantitation in M-mode echocardiography Result of a survey of echocardiographic measurements *Circulation* 1978,58:1072–83

7 Tomura S, Oono Y, Kuriyama R, Kuriyama R, Takeuchi J Plasma concentration of fibrinopeptide A and fibronopeptide Bβ15–42 in glomerulonephritis and the nephrotic syndrome. *Arch Intern Med* 1985;145 1033–5

8 Rylatt DB, Blake AS, Cottis LE, *et al* An immunoassay for human D dimer using monoclonal antibodies *Thromb Res* 1983,31·767–78.

9 WHO expert committee on biological standardization 28th report *WHO Tech Rep Ser* 1977,610 45–51

10 Voorthuizen HV, Kluft C. Improved assay conditions for automated antithrombin III determinations with the chromogenic substrate S-2238 *Thromb Haemost* 1984, 52·350–3

11 Yamaguchi T, Minematsu K, Choki J, Ikeda M Clinical and neuroradiological analysis of thrombotic and embolic cerebral infarction *Jpn Circ J* 1984,48 50–8

12 Cerebral embolism task force Cardiogenic brain embolism *Arch Neurol* 1986,43 71–84

13 Askey JM, Bernstein S The management of rheumatic heart disease in relation to systemic arterial embolism *Prog Cardiovasc Dis* 1960;3 220–32

14 Daniel WG, Nellessenn U, Schroder E, *et al* Left atrial spontaneous echo contrast in mitral valve disease an indicator for an increased thromboembolic risk *J Am Coll Cardiol* 1988,11 1204–11

15 Fukuda Y, Nakamura K The incidence of thromboembolism and hemocoagulative background in patients with rheumatic heart disease *Jpn Circ J* 1984,48 59–66

16 Okada Y, Yamaguchi T, Minematsu K, *et al* Hemorrhagic transformation in cerebral embolism *Stroke* 1989,20 598–603

17 Yasaka M, Yamaguchi T, Miyashita T, *et al* Predisposing factors of recurrent embolization in cardiogenic cerebral embolism *Stroke* 1990,21 1000–7

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Familial Ebstein's anomaly: a report of six cases in two generations associated with mild skeletal abnormalities

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Abstract

In a family of 11 persons in three generations six had Ebstein's anomaly. Five of the six showed mild skeletal anomalies—that is, restricted finger extension, with or without limitation of larger joints, and externally rotated little toes. Two other members of the family had the skeletal features without Ebstein's anomaly.

The findings suggest a dominantly inherited syndrome of Ebstein's anomaly and skeletal abnormalities. The four female patients were all mildly affected whereas three of the four male patients were severely affected.

There have been several reports of Ebstein's anomaly occurring in two people from the same family.[1-3] Emanuel *et al* reviewed the published reports and examined the first degree relatives of 26 patients with Ebstein's anomaly but found no familial cases.[4] Watson conducted an international cooperative study of 505 cases and found only two examples of familial incidence, both in siblings.[5] We report a family in which eight people in three generations had either Ebstein's anomaly or a characteristic pattern of mild skeletal anomalies or both.

Case reports

The index patient 2c presented in 1962 at the age of five years with an asymptomatic heart murmur that was diagnosed as Ebstein's anomaly on clinical examination; this was confirmed three years later at cardiac catheterisation. After she and her sister had had a total of five children we examined the entire family clinically and with chest *x* ray, electrocardiogram, and echocardiogram (Doppler and colour flow mapping). Figure 1 and the table summarise the pedigree of this family. A brief summary of each member follows.

1a—He was thought to have a "weak heart" when young and was not accepted for military service. At the age of 62 years he underwent aortic valve replacement for aortic stenosis. Preoperative evaluation included cardiac catheterisation; no right heart abnormalities were found. His echocardiogram was normal but the electrocardiogram showed atrial fibrillation. On examination, extension of his fingers was found to be limited (fig 2) and was accompanied by tightening and furrowing of the palmar fascia that resembled Dupuytren's contracture. There was limited mobility of the interphalangeal joints of the thumbs, and his little toes were proximally placed and externally rotated (fig 3).

1b—She is the wife of 1a. She was symptom free with no evidence of Ebstein's anomaly and with no skeletal abnormalities.

2b was symptom free with no clinical or echocardiographic evidence of Ebstein's anomaly. We found that extension of the little fingers was restricted at the proximal interphalangeal joints (fig 2) with tightening and furrowing of the palmar fascia as seen in 1a. Elbow extension was also restricted. Her feet were high arched with overlapping of the right second and third toes, but the little toes were not externally rotated.

2a—Is the non-consanguineous husband of 2b. He showed no evidence of Ebstein's anomaly.

3a was symptom free and had a normal electrocardiogram. Chest *x* ray showed a cardiothoracic ratio of 0·5 and a prominent right atrial shadow on the right heart border. Echocardiography showed mild Ebstein's anomaly with small and tethered tricuspid valve septal leaflet and moderate tricuspid regurgitation. The little toes were proximally placed but there was no joint restriction.

3b was born at 33 weeks' gestation with hydrops fetalis. Echocardiography showed severe Ebstein's anomaly with no flow into the pulmonary arteries. He remained acidotic, cyanosed, poorly perfused, and anuric despite maximal support including intermittent positive pressure ventilation, dopamine and prostaglandin infusions, and paracentesis of

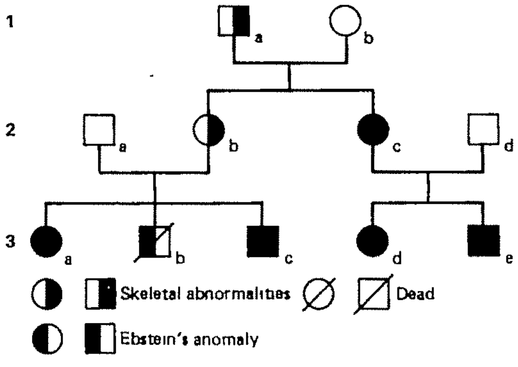

Figure 1 Pedigree of family in which some members had Ebstein's anomaly.

Findings in the family examined

Case	*Age (yr)*	*Ebstein's anomaly*	*Symptoms*	*Joint contractures*	*Toes abnormal*
1a	67	No		+	+
1b	64	No		–	–
2a	31	No		–	–
2b	32	No		+	+
3a	5	Yes	No	–	+
3b	ND	Yes	Yes	–	–
3c	1 mnth	Yes	Yes	+	+
2c	30	Yes	No	+	+
2d	30	No	–	–	–
3d	7	Yes	No	+	+
3e	3	Yes	Yes	+	+

ND, neonatal death.

the pleural and peritoneal cavities. He died aged one day and necropsy confirmed the diagnosis. No skeletal abnormalities were noted.

3c presented in the neonatal period with cyanosis and signs of heart failure. Echocardiography showed mild Ebstein's anomaly and he improved with oxygen and diuretics. He had simian creases and limitation of extension of the metacarpophalangeal joints by palmar soft tissues, but no limitation of other joints. His little toes were proximally placed and externally rotated (fig 3).

2c—An asymptomatic cardiac murmur was detected when she was five years old. A clinical diagnosis of Ebstein's anomaly was made which was confirmed at cardiac catheterisation when she was eight years old. She remains symptom free and experienced no cardiac problems during her pregnancies. Echocardiography showed a large right atrium, small right ventricle, and moderate tricuspid regurgitation. She had restricted extension of all fingers, similar to 1a and 2b, plus limitation of elbow extension. Her feet were high arched and the little toes were short and externally rotated (fig 3).

2d is the non-consanguineous husband of 2c, in whom all findings were normal.

3d was symptom free with no evidence of cardiac problems on clinical, *x* ray, and electrocardiographic examination. Echocardiography showed mild Ebstein's anomaly with apical displacement of the septal leaflet of the tricuspid valve and mild tricuspid regurgitation. Finger extension was limited as in 1a and 2b, and ankle mobility was slightly reduced. Her little toes were externally rotated.

3e—He presented as a neonate with cyanosis and cardiac failure. Echocardiography at this time showed severe Ebstein's anomaly. He remained symptomatic with shortness of breath on exertion. Echocardiography when he was three years old showed a large right atrium, small right ventricle, and moderate tricuspid stenosis and regurgitation. The mitral valve was also abnormal with mild mitral stenosis and a thickened valve that appeared to be dysplastic. Extension of knees, elbows, fingers, and hands were restricted (as in 1a and 2b), and also abduction of the hips. His calves were slightly wasted but no neurological abnormalities were detected. His feet were high arched and his little toes were externally rotated (fig 3). His thumbs were broad and short.

None of the family showed abnormalities on examination of the nervous system. There was no evidence of pre-excitation or Wolff-Parkinson-White syndrome on the electrocardiogram.

Discussion

Familial Ebstein's anomaly is rare. Gueron *et al*

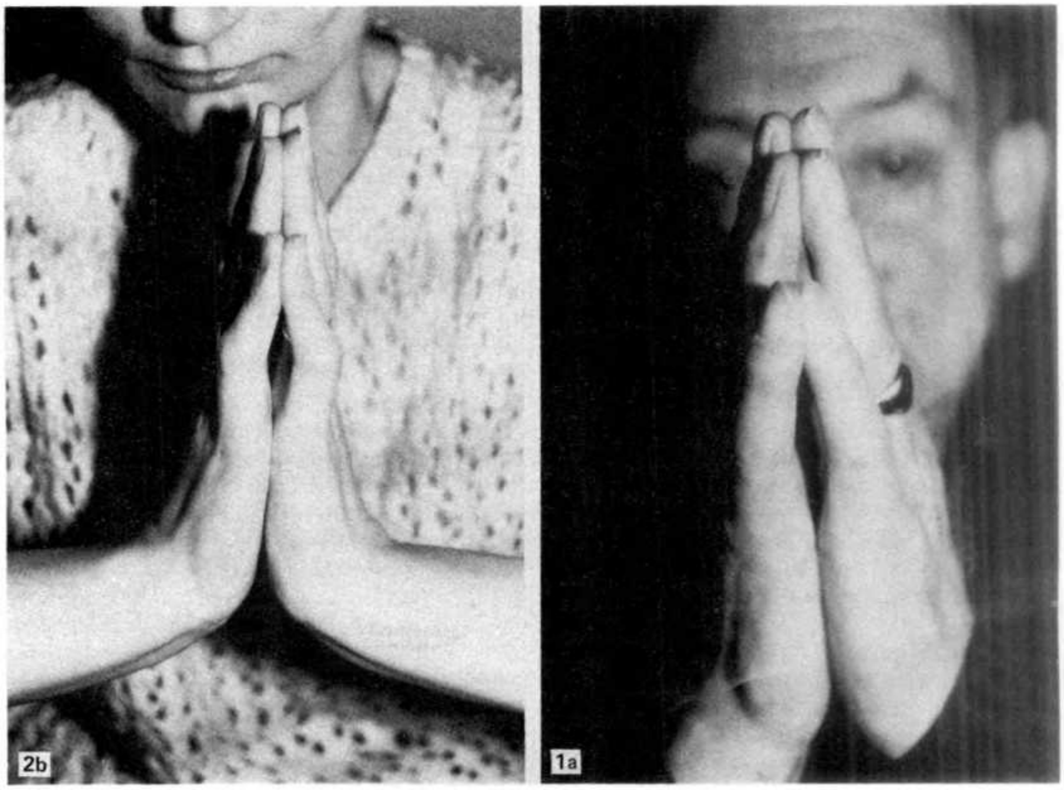

Figure 2 Limitation of extension of proximal interphalangeal joints in 2b (left) and 1a (right).

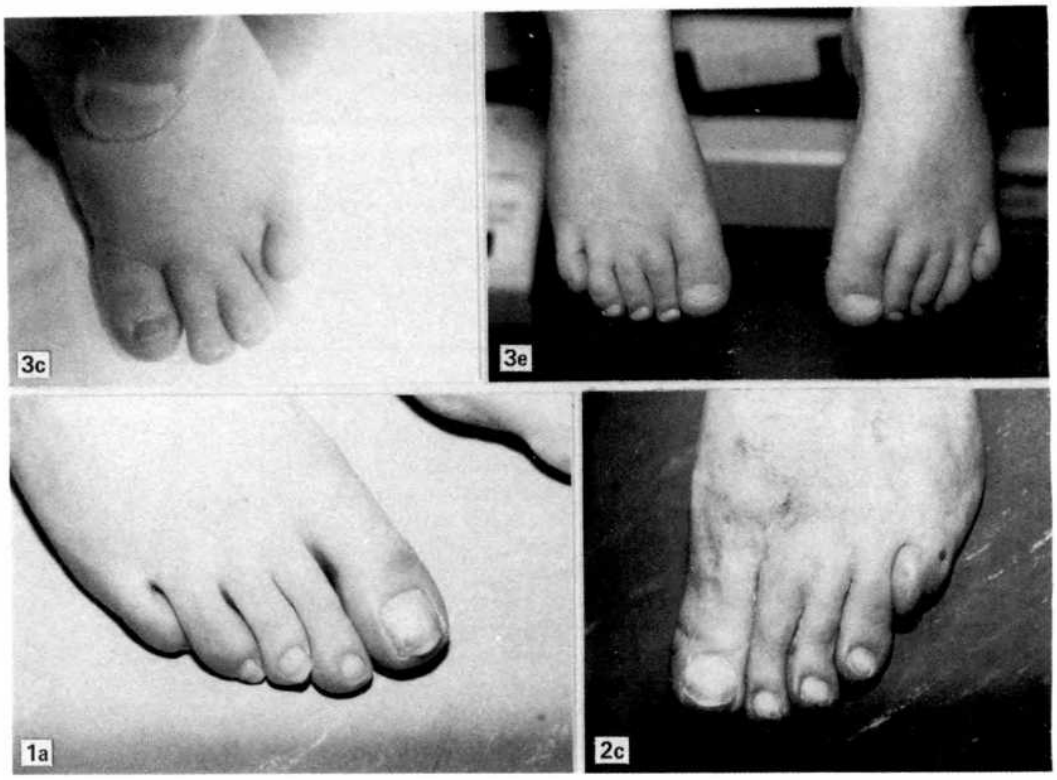

Figure 3 Proximally placed and externally rotated little toes in 3c, 3e, 1a, and 2c.

reported a 20 year old man and his sister aged 12, who were born to second cousins, and who both died of Ebstein's anomaly.[1] Donegan *et al* reported the condition in a boy and his maternal uncle.[2] Simcha and Bonham-Carter reported two families; in one two brothers were affected and in the other a father and daughter were affected.[3] Watson in a large international cooperative study of 505 cases could only find two examples of siblings with this condition.[5] Our report is, therefore, to our knowledge, the largest of its kind.

Extracardiac abnormalities have been reported in association with Ebstein's anomaly, most notably by Siebert *et al* who described four unrelated cases in which Ebstein's anomaly occurred as part of a syndrome of multiple malformations.[6] All four were different and none resembled our cases. Case 4 seems to have the OEIS syndrome (omphalocele, exstrophy, imperforate anus, and spinal defects).[7]

The skeletal abnormalities in the family we studied seem to be familial traits, but it is not clear whether they are part of an inherited syndrome that includes Ebstein's anomaly as a feature, or whether they are coincidental. The findings in the hands resembled Dupuytren's contracture, but were congenital and nonprogressive.

The most likely mechanism for the inheritance of Ebstein's anomaly in this family is autosomal dominance. Males were more severely affected than females. The degree of variability in the male cases makes X-linkage unlikely, but in the absence of male to male transmission this cannot be excluded.

This family also shows that Ebstein's anomaly continues to be a poorly understood cardiac problem with a wide spectrum of clinical presentation. Watson suggested that most patients are either symptom free or have only slight symptoms.[5] This may mean that the incidence of familial cases is underestimated.

There is a need for a systematic study of Ebstein's anomaly by echocardiography and Doppler techniques to determine what proportion of those who present clinically have mildly affected relatives and to define the anatomical features of the milder defects.

1 Gueron M, Hirsch M, Stern J, Cohen W, Levy MJ. Familial Ebstein's anomaly with emphasis on surgical treatment. *Am J Cardiol* 1966;**8**:105–11.

2 Donegan CC, Moore MM, Wiley TM, Hernandez FA, Green JR, Schiebler GL. Familial Ebstein's anomaly of the tricuspid valve. *Am Heart J* 1968;**75**:375–9.

3 Simcha A, Bonham-Carter RE. Ebstein's anomaly: clinical study of 32 patients in childhood. *Br Heart J* 1971;**33**:46–9.

4 Emanuel R, O'Brien K, Ng R. Ebstein's anomaly: genetic study of 26 families. *Br Heart J* 1976;**38**:5–7.

5 Watson H. Natural history of Ebstein's anomaly of tricuspid valve in childhood and adolescence: an international cooperative study of 505 cases. *Br Heart J* 1974;**36**:417–27.

6 Siebert JR, Barr M, Jackson JC, Benjamin DR. Ebstein's anomaly and extracardiac defects. *Am J Dis Child* 1989;**143**:570–2.

7 Carey JC, Greenbaum B, Hall BD. The OEIS complex (omphalocele, exstrophy, imperforate anus, spinal defects). *Birth Defects* 1978;**14(6B)**:253–63.

Br Heart J 1991;66 29–35

EPIDEMIOLOGY

Influence of racial origin on admission rates of patients with suspected myocardial infarction in Birmingham

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Abstract
All patients with suspected myocardial infarction admitted to hospital in four Birmingham health districts were studied to test the hypothesis that Asian patients would be overrepresented and Caribbean patients underrepresented compared with the indigenous population. One thousand four hundred and ninety six patients had a final diagnosis of myocardial infarction or severe angina pectoris. The relative risk of admission for Asian men compared with white men aged 45–64 years was 2·65 (95% confidence interval 2·20 to 3·19) and the risk for Asian men was high for both myocardial infarction and ischaemia when analysed separately. The relative risk of admission for Caribbean men compared with white men was 0·53 (95% CI 0·33 to 1·20). The relative risk for Asian women compared with white women in the same age group was 2·58 (95% CI 1·68 to 3·96), but this was due to an excess of admissions diagnosed as ischaemia rather than infarction in the Asian women. For Caribbean and white women the risk of admission was the same, although significantly fewer Caribbean women were admitted with myocardial infarction. The study was undertaken in 1986–87 and population data had to be derived from the 1981 census. The resident population changed in those five years and so the results were recalculated making allowances for these changes in the health districts involved. Based on these data the admission rate for Asian men with suspected myocardial infarction aged 45–64 was nearly twice that for white men (1·8): the relative risk of admission for Asian men compared with white men was 2·04 (95% CI 1·53 to 2·18). For Caribbean men the relative risk compared with white men was 0·45 (95% CI 0·29 to 0·71). For Asian women the relative risk of admission calculated from the adjusted census data resembled that in white women aged 45–64 years. The relative risk for admission with coronary heart disease in Asians is higher than expected from previous reported work; one possible explanation for this is that the Asian population resident in the area under study was larger than estimated. The single major difference in risk factors was the high prevalence of diabetes mellitus in Asians (19·5% compared with 8·3% for white residents) but this did not wholly account for the excess of admissions from the Asian community.

Though as a general rule emigrants are healthier than the population left behind[1] their mortality from cardiovascular disease tends to be intermediate between that of their home country and the land of adoption.[2] Within one or two generations, however, the pattern of mortality changes towards that of the adopted country, as shown by westernised Japanese-Americans.[3] Although the incidence of coronary artery disease in India and Pakistan is not well documented, these rates are believed to be lower than those found in Britain so that the high mortality from coronary disease seen in Asians exceeds both that of the indigenous white population in Britain and their region of origin.[4–6] High mortality from coronary disease in Indian migrants has also been reported from other parts of the world[7 8] whereas the prevalence of coronary artery disease in black people both in the West Indies and in their country of adoption is less[1 9]; none the less in the United States of America mortality from coronary artery disease in black men is similar to that of white men, though it may be excessive in black women.[10 11] The city of Birmingham has large Asian and Caribbean communities and offered the opportunity to observe whether the expected excess of coronary disease in Asians and the anticipated low prevalence in Caribbeans compared with the indigenous white population were reflected in different hospital admission rates for suspected myocardial infarction and to explore reasons for any observed differences.

Patients and methods

Patients were studied from 1 July 1986 to 30 June 1987 in five hospitals in four health districts with a total population of 0·84 million. Only patients under the age of 65 years and

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normally resident within the health districts were included. Our data relate to all patients in whom a diagnosis of myocardial infarction was suspected and in whom the final diagnosis was one of cardiac pain caused by coronary disease. Myocardial infarction was confirmed by the development of typical electrocardiographic changes and/or a rise in cardiac enzymes to at least twice the upper limit of the normal range for the hospital concerned. If infarction was not confirmed and the diagnosis of coronary ischaemia could not be substantiated patients were excluded from the study. Details of age, sex, occupation, address, ethnic origin, risk factors, and past medical history were recorded on admission. Details of blood cholesterol (if measured on day 1 of admission), final outcome, and final diagnosis as assessed by the medical team in charge of the patient were recorded after discharge, death, or transfer from hospital. The information was collected by doctors and nurses working on the coronary care units or the emergency admission units.

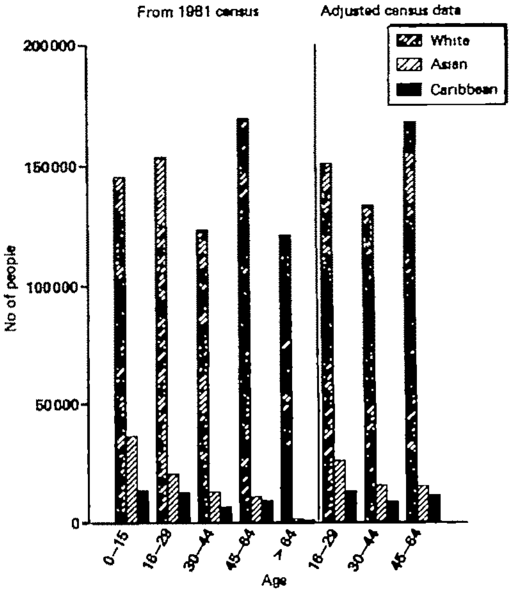

Figure 1 Population of three racial groups by age in years from 1981 census and according to adjusted census data.

The estimate of the population at risk was calculated from the 1981 census using Small Area Statistics which records the number of persons usually resident in private households whether born inside or outside the United Kingdom categorised by age and sex of residents, and by birthplace of head of household for each electoral ward contained within the four health districts in the study.[12] Narrower age bands of five or 10 years are not available for individual wards. The white group included all those born in Great Britain, Northern Ireland, and the Republic of Ireland, the Asian group included all those born in the Indian subcontinent, and the Caribbean group all those born in the West Indies. Total population statistics were calculated for the three racial groups according to sex, and separate totals were obtained for those between the ages of 30 and 44 years, and 45 and 64 years. The age and sex structure of the three communities differed considerably with a relative excess of men in the Asian group; for example, in the 45–64 age group, the male:female ratio was 0·98:1 for white residents, 1·1:1 for Caribbeans, and 1·6:1 for Asians. In view of these differences most results are expressed according to sex. The Asian and Caribbean populations are young with very few members over the age of 65 years unlike the aging white population (fig 1). In the five years since the population census, the numbers of Asians and Caribbeans entering the 30–44 age group have been greater than the number leaving the 45–64 age group. In view of this, the admission rate with myocardial infarction or myocardial ischaemia was calculated in two ways; firstly on the population data of 1981 and secondly on an adjusted population base. The adjustment assumed that between 1981 and 1986 one third of the people in the 30–44 age group moved into the 45–64 age group. It was also assumed that one quarter of the white population moved out of the 45–64 age group, but because the Asian and Caribbean populations had few people in the older groups, none was assumed to have moved out of the 45–64 age group. This calculation would almost certainly result in an overestimate of the Asian and Caribbean population at risk (fig 1). The adjustment gave an estimated population of 83 481 white men, 9200 Asian men, and 5923 Caribbean men, and 85 427 white women, 5930 Asian women, and 5356 Caribbean women in the 45–64 age group. There are no good data on changes in the number of Birmingham citizens from the New Commonwealth and Pakistan (NCWP), or indeed of any other city or district within the United Kingdom, between 1981 and 1986. One estimate suggests an annual national increase in citizens of NCWP origin of 90 000, mostly from South Asia.[13] Two thirds of the increase is accounted for by births; when allowance is made for deaths the figure is approximately 140 000 new migrants over the five years. Between 1983 and 1985 the West Midlands contained an average of 20% of the citizens of South Asian origin living within the United Kingdom.[13] If it is assumed that a similar proportion of the new migrants entered this region a population increase of 28 000 would be predicted. Approximately 25% of the West Midlands NCWP population was housed in Birmingham[14] suggesting a possible increase of around 12 300 even though we know that the overall population of Birmingham has fallen by 20 000 during the same five year period.[15] If the migrants had an age and sex distribution similar to the existing population an increase of around 1600 between the ages of 45 and 64 would be expected of whom two thirds would be men—about 1070. This is likely to be an overestimate because the expected pattern of migration was thought to involve predominantly the female partners of those already within the United Kingdom. This would finally adjust the figure for Asian men aged 45–64 to 10 270 and that for women to 6460.

Differences between the populations based on actual numbers were assessed by the χ^2 test and 95% confidence intervals (95% CI) for relative risk were calculated. Differences in prevalence of risk factors were assessed by the

Table 1 Demographic data

Group	Population 1981 census		Admissions		Number of confirmed infarctions		Number aged 45–64 years				Deaths	
							Male		Female			
	Male	Female	Male	Female	Male	Female	Population	Admissions	Population	Admissions	All ages (male)	45–64 years (female)
White	348 082	366 023	897	391	606	232	82 806	596	87 488	206	115 (73)	71 (42)
Asian	44 426	37 746	184	36	122	15	7024	134	3782	23	15 (14)	13 (12)
Caribbean	20 875	21 991	24	6	15	3	5005	19	4090	4	1 (0)	1 (0)

standard error of the difference between the proportions of each risk factor between the groups. Cholesterol concentrations were assessed by Student's unpaired *t* test.

Results

We studied 1496 patients judged to have a final diagnosis of myocardial infarction or severe angina pectoris. Table 1 records the relevant demographic data for the study.

ALL MALE PATIENTS

The indigenous white male population had 897 admissions with suspected myocardial infarction, an admission rate of 258/100 000 white population. One hundred and eighty four Asian men were admitted, an admission rate of 414/100 000, and from the Caribbean community only 24 men were admitted, an admission rate of 115/100 000 population. Compared with the white population only 114 Asian admissions would have been expected but there were 184 ($p < 0{\cdot}001$); this contrasts with 53 expected admissions from the Caribbean community, where there were only 24 ($p < 0{\cdot}001$).

The admission rate for definite myocardial infarction was 71/100 000 for white residents, 275/100 000 for Asian residents, and 72/100 000 for Caribbean residents. There was a significant difference in the admission rate between Asian residents and white residents ($p < 0{\cdot}001$).

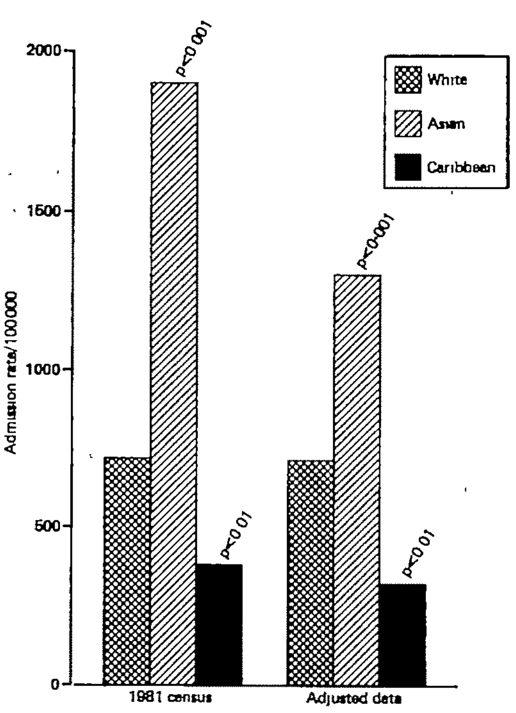

Figure 2 Admission rate for suspected myocardial infarction in each racial group/100 000 population aged 45–64 years according to 1981 census data and adjusted population data for men.

MEN AGED 45–64 YEARS

Most patients admitted in the study were in the 45–64 age group (66%). For men in this age group, the differences in admission rate per 100 000 population when either the 1981 census data or the adjusted census data were used remained highly significant (fig 2). With the 1981 census data, there were 720/100 000 admissions in the white group, 1908/100 000 in the Asian group, and 380/100 000 admissions in the Caribbean group. The adjusted census data gave admission rates of 714/100 000 for white residents, 1304/100 000 for Asian residents, and 321/100 000 for Caribbean residents. The admission rate per 100 000 population from the Asian community was 2·7 times the admission rate from among the white residents ($p < 0{\cdot}001$) calculated from the 1981 census data and 1·8 times the admission rate calculated from the adjusted census data ($p < 0{\cdot}001$). The relative risk of admission from suspected myocardial infarction for Asian men compared with white men was 2·65 (95% CI 2·20 to 3·19) when the 1981 census data were used and 2·04 (95% CI 1·53 to 2·18) when the adjusted population data were used. The

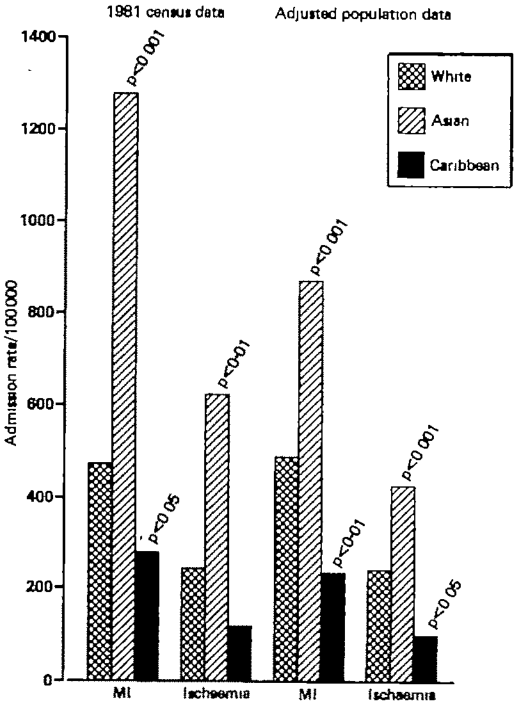

Figure 3 Admission rate for men in each racial group/100 000 population aged 45–64 years for confirmed myocardial infarction (MI) and acute myocardial ischaemia according to 1981 census data and adjusted population data.

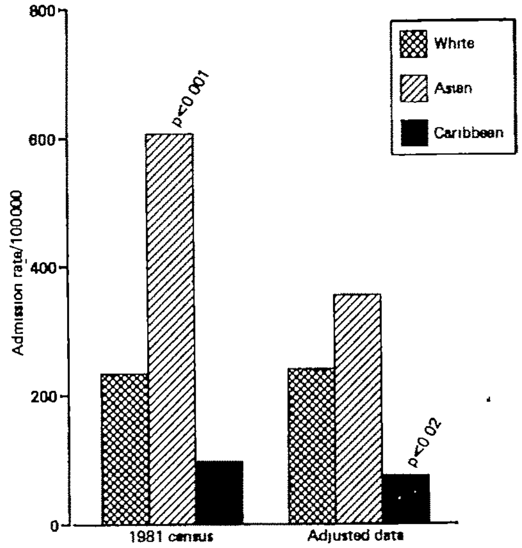

Figure 4 Admission rate for suspected myocardial infarction in each racial group/100 000 population aged 45–64 years according to 1981 census data and adjusted population data for women.

Caribbeans were underrepresented compared with the white community when the 1981 census data were used ($p < 0{\cdot}01$) and when the adjusted data were used ($p < 0{\cdot}001$). For Caribbeans, the relative risk compared with white residents was 0·53 (95% CI 0·33 to 1·20) when the 1981 census data were used and 0·45 (95% CI 0·29 to 0·71) when the adjusted population data were used.

When the results for myocardial infarction and myocardial ischaemia are analysed separately the same pattern emerges (fig 3): 393 white residents, 90 Asians, and 14 Caribbeans had a definite infarct. The admission rate per 100 000 for definite myocardial infarction was 475 for white residents, 1281 for Asians, and 280 for Caribbeans when the 1981 census data were used, and 491, 876, and 236 respectively when the adjusted census data were used. The corresponding admission rates per 100 000 for ischaemia were 245, 626, and 120; and 243, 428, and 101. For myocardial infarction and myocardial ischaemia, when both the 1981 census data and the adjusted data were used, the admission rate from the Asian community was higher than expected when compared with the white community ($p < 0{\cdot}001$ for each comparison). The relative risk of being admitted with a definite myocardial infarct for Asian men aged 45–64 compared with white men was 2·70 (95% CI 2·15 to 3·39) when the 1981 census data were used and 1·86 (95% CI 1·48 to 2·33) when the adjusted population data were used. In the Caribbean community the difference was not significantly different for ischaemia alone when the 1981 census data were used but it was significantly less than expected compared with the indigenous white population for myocardial infarction when the 1981 census data were used ($p < 0{\cdot}05$) and for myocardial infarction ($p < 0{\cdot}01$) and ischaemia ($p < 0{\cdot}05$) when the adjusted census data were used. The relative risk of myocardial infarction in Caribbeans compared with the white residents when the census data for 1981 were used was 0·59 (95% CI 0·35 to 1·00) and when the adjusted data were used it was 0·50 (95% CI 0·29 to 0·85). The case fatality rate per 100 admissions with suspected myocardial infarction in men aged 45–64 was not significantly different in the Asian and white groups (table 1).

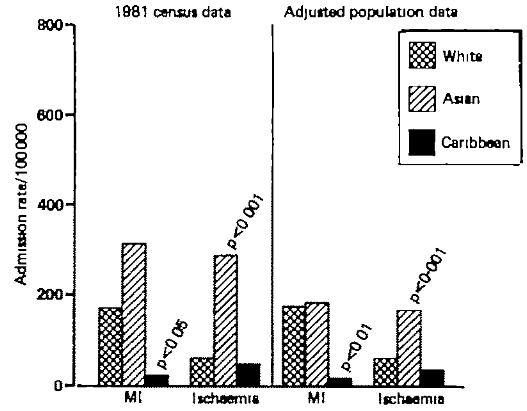

Figure 5 Admission rate for women in each racial group/100 000 population aged 45–64 years for confirmed myocardial infarction (MI) and acute myocardial ischaemia according to 1981 census data and adjusted population data.

ALL FEMALE PATIENTS

The admission rate per 100 000 for white women was 107, and this did not differ significantly from the admission rate for Asian women (95). The admission rate (27) for Caribbean women was significantly lower than that for white women ($p < 0{\cdot}001$). Similar findings were seen in those patients admitted with definite infarction: the admission rate was 63 for white women, 40 for Asian women, and 14 for Caribbean women ($p < 0{\cdot}001$ for Caribbean women compared with white women).

WOMEN AGED 45–64

For the 1981 census data the admission rate per 100 000 for Asian women was higher than for white women (608 *v* 235 ($p < 0{\cdot}001$)); the relative risk of admission was 2·58 (95% CI 1·68 to 3·96) (fig 4). The admission rate for the Caribbean group (98) was not significantly different. When the adjusted census data were used the admission rate in Asian women was not significantly different from that in white women. The admission rate for Caribbean women was significantly less (75) than that in white women ($p < 0{\cdot}02$).

There was no significant difference in admission rates for definite myocardial infarction between Asian and white women either for the 1981 census data or the adjusted data (fig 5). Significantly fewer Caribbean women were admitted ($p < 0{\cdot}05$).

According to the 1981 census data significantly more Asian women than white women were admitted with myocardial ischaemia ($p < 0{\cdot}001$). The case fatality rate was similar in all three groups.

RISK FACTORS

Sixty per cent of the Caribbean patient group had hypertension: this prevalence of hypertension was significantly greater than that found in either the white or the Asian groups ($p < 0{\cdot}001$); a high prevalence of diabetes mellitus was also found in the Caribbean group although this difference was not significant (table 2). Of the Asian patients 19·5% had diabetes mellitus, a significantly higher pre-

Table 2 Numbers of patients admitted with risk factors (percentage of total admissions)

	Hypertension	*Diabetes mellitus*	*Smoking*	*Ex-smoker*	*Lifelong non-smoker*	*Total number in group*
White						
All patients	278 (22·3)	103 (8·3)	588 (47·1)	381 (30·6)	256 (20·5)	1246
Male (45–64 years)	120 (20·1)	47 (7·9)	315 (52·9)	188 (31·5)	84 (14·1)	596
Female (45–64 years)	60 (29·1)	14 (6·8)	94 (45·6)	50 (24·3)	56 (27·2)	206
Asian						
All patients	56 (25·5)	43 (19·5)	104 (47·3)	32 (14·5)	82 (37·3)	220
Male (45–64 years)	26 (19·4)	25 (18·7)	76 (56·7)	24 (17·9)	32 (23·9)	134
Female (45–64 years)	13 (56·5)	9 (39·1)	1 (4·3)	0	22 (95·7)	23
Caribbean						
All patients	18 (60·0)	7 (23·3)	10 (33·3)	9 (30·0)	11 (36·7)	30

valence of diabetes mellitus than in the white patients (8·3%) (p < 0·001). It is difficult to standardise for this risk factor when the frequency of diabetes in the base population is unknown but the relative risk of admission in non-diabetics can be calculated by referring to the overall population: this gives a relative risk of 2·34 (95% CI 0·56 to 9·718) in Asian men aged 45–64 years compared with white men. For non-diabetic Asian women in this age group the relative risk was 0·85 (95% CI 0·50 to 1·45).

Different smoking trends were observed. The numbers of current smokers were similar but there was a significantly greater proportion of lifetime non-smokers in the Asian group (p < 0·001) and a larger number of ex-smokers in the white group (p < 0·01) and West Indian group (NS). The mean (SEM) cholesterol concentration in 384 white patients was 6·68 (0·33) mmol/l. There were no significant differences between the groups even after adjustment for age. Asian women had a significantly higher prevalence of hypertension and diabetes than Asian men and both white men and women (p < 0·001 for all groups).

Although the inpatient Asian population was broadly similar to that of the total Asian community for region of origin, there was a trend towards overrepresentation of Pakistani Moslems and underrepresentation of Indian Hindus and Sikhs (fig 6). The prevalence of diabetes mellitus was similar among patients in all subgroups of the Asian population (between 20% and 40%).

PAST MEDICAL HISTORY

The only significant difference was that a history of angina was more common in the white group than the Asian group (p < 0·05).

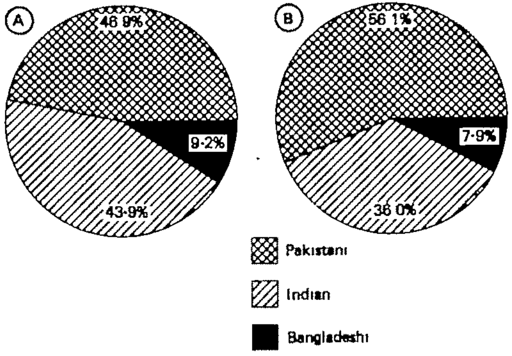

Figure 6 Proportion of main Asian ethnic groups in Birmingham: (A) aged ≥30 years in the community (B) aged ≥30 years admitted to hospital.

Discussion

This study confirms a high incidence of coronary events requiring hospital admission in people from the Indian subcontinent living in Britain, which contrasts with the lower incidence seen among West Indians.[16] This accords with earlier studies from the United Kingdom[17–19] and other parts of the world,[6 9] although the relative risk (2·04) seen for Asian men aged 45–64 was greater than in other studies where it ranged from 1·2 to 1·5.[17–19] This could reflect an inaccuracy in the calculation of the resident Asian population under study. There are major difficulties in obtaining an accurate picture of the racial make up of the population in a large conurbation at any one time. We adjusted the census data on the basis of migration figures but these calculations involve much supposition which cannot be validated. Outmigration—that is members of the Asian community leaving the area since 1981—cannot be calculated but any such reduction in numbers would reduce the population at risk. Immigration, in particular the growth of the Asian population over the five year period since the census was taken, is difficult to calculate. We attempted to allow for this but all the figures can only be likely estimates based on the crude data.[13–15] We would have preferred to analyse the data in narrower age bands and so reduce error in population shifts by age but no such data are available in Small Area Statistics for political wards. We thought that the error introduced into the denominator by the use of population data for five year age bands either for Birmingham alone or for the whole of the West Midlands would have been greater. The Asian community is substantially younger than the indigenous white population and if five year age bands are not used this difference introduces further inaccuracies. We believe there would be a greater proportion of the population in the lower end of the 45–64 range. We therefore assumed that there was no loss of Asian population from this range in the group aged ≥65 years. Both this allowance and the assumption that one third of the population would have moved from the 30–44 years age group, which is probably an overestimate, tend to exaggerate the true population of the Asians aged 45–64 years. Such a bias would tend to underestimate the difference that we found in the admission rates. It might have been helpful to look at comparative data for a disease for which Asians would be expected to have a lower age standardised admission rate than white residents, for example, cancer. However, information on death or diagnosis of cancer on discharge from hospital was not recorded by ethnic origin either on the cancer registry or by the individual health authorities.

The patients in this study were seen in emergency admitting units and coronary care units but a few patients with chest pain were admitted to other wards and included. It is likely that some patients with coronary disease who had a myocardial infarction were not identified as such on presentation and were admitted to wards other than a coronary care unit, the diagnosis becoming apparent later in their hospital stay. Again, these numbers will be small because doctors tend to err on the side of caution when dealing with chest pain—when myocardial infarction is suspected overdiagnosis is more common than underdiagnosis. No account was made of patients seen in the casualty department and sent home. By documenting every patient's address, we have been able to identify and exclude patients living outside the study area, but have been unable to identify patients resident in the area of the study who have been treated in hospitals outside the four health districts involved. This is unlikely to be a large number, however, because of the ambulance policy which is to take all patients with suspected myocardial infarction to the nearest hospital. It is likely that some people who lived within the area were admitted from their place of work situated outside the four districts during the working day but the large contiguous area covered by the four health districts in the study would minimise this source of error.

It is true that the hospital population may not entirely reflect the community prevalence of coronary disease but this study was concerned with the impact on the hospital service of racial variations in the disease.

Asian men had a high admission rate for coronary disease compared with the indigenous white population. Asian women, however, were overrepresented only in the group with ischaemia and it may be that difficulties in communication and understanding have resulted in some women being incorrectly diagnosed; where there was a hard end point of myocardial infarction, there was no increase in admission rate, unlike the results for Asian men. A broad overview of risk factors confirmed that a greater number of Asians are lifetime non-smokers though the prevalence of smoking in Asian men aged 45–64 years was the same as in white men. Unlike white women, very few Asian women smoke. This accords with other studies.[20 21] The high prevalence of diabetes mellitus is not surprising in view of previous reports[8 21] and its known prevalence in the Asian community.[18 22] A prevalence of diabetes mellitus of approximately 6% has been reported in Asians aged 45–49 years rising to an excess of 12% in 60–69 year old Asians, about five times the rate seen in white people.[22] Our study found a prevalence of 19·5% diabetes among Asian patients and this may go some way to explain the higher incidence of acute coronary events in this section of the population. The relative risk in non-diabetic Asian men was also high compared with white men. Conversely, Asian women did not have a high relative risk of admission but the prevalence of diabetes was high in the patient group. This suggests that diabetes alone cannot account for the differences in admission rates. If the population estimate is higher than that calculated, however, the prevalence of diabetes mellitus might account for more of the increased risk. As in this study, others have not found high cholesterol concentrations in Asian patients with coronary disease[8] or in the Asian population[19]; however, only total serum cholesterol was measured and only a third of all patients had their cholesterol measured on admission.

The lower admission rate among people of Caribbean origin described here is compatible with their recorded low mortality for coronary artery disease. Among those who were admitted with suspected myocardial infarction there was a high prevalence of diabetes but numbers were small and did not achieve statistical significance. Hypertension, however, was more prevalent in the Caribbean patients than in the other two groups. This study did not help to clarify why Caribbeans have such a low risk of coronary artery disease.

The admission rate to hospital for confirmed myocardial infarction or myocardial ischaemia among Asian men in Birmingham was higher than that of the indigenous white population. The single major difference in risk factors was the high prevalence of diabetes mellitus in all Asian groups,[18] a higher prevalence than would be expected in the Asian community. The morbidity resulting from diabetes mellitus and coronary disease represents a considerable problem in the Asian community and this is going to increase as this young population ages and if the attendant high admission rate to hospital continues.

We thank all the nurses and physicians of the coronary care units and emergency admitting units involved in this study.

1 Marmot MG, Adelstein AM, Bulusu L. Cardiovascular mortality among immigrants to England and Wales. *Postgrad Med J* 1981;57 760–2.
2 Marmot MG, Adelstein AM, Bulusu L. *Immigrant mortality in England and Wales 1970–1978*. London: HMSO, 1984. (OPCS Studies on Medical and Population Subjects, No 47.)
3 Marmot MG, Syme SL. Acculturation and coronary heart disease in Japanese-Americans. *Am J Epidemiol* 1976, 104 225–47.
4 *Coronary heart disease and Asians in Britain*. London: Confederation of Indian Organisations (UK) and the Coronary Prevention Group, 1986.
5 Miller GJ, Beckles GLA, Alexis SD, Byam NTD, Price SGL. Serum lipoproteins and susceptibility of men of Indian descent to coronary heart disease. *Lancet* 1982,ii 200–3.
6 Seedat YK. Hypertension and ischaemic heart disease in Indian people living in South Africa and in India. *S Afr Med J* 1982;61 965–7
7 Danaraj TJ, Acker MS, Danaraj W, Ong WH, Yam TB. Ethnic group differences in coronary heart disease in Singapore. an analysis of necropsy records. *Am Heart J* 1959;58:516–26.
8 Beckles GLA, Miller GJ, Kirkwood BR, Alexis SD, Carson DC, Byjam NTA. High total and cardiovascular disease mortality in adults of Indian descent in Trinidad unexplained by major coronary risk factors. *Lancet* 1986;i.1298–300
9 Kraus JF, Borhani NO, Franti CE. Socioeconomic status, ethnicity, and risk of coronary heart disease. *Am J*

Epidemiol 1980;111·407–14.

10 Gillum RF. Coronary heart disease in black populations I. Mortality and morbidity. *Am Heart J* 1982;104:839–51.

11 Johnson JL, Heineman EF, Heiss G, Hames CG, Tyroler HA Cardiovascular disease risk factors and mortality among black women and white women aged 40–64 years in Evans County, Georgia. *Am J Epidemiol* 1986,123·209–20.

12 OPCS. *Small area statistics 1981*. Draft tables 8822/8823. 1–84.

13 OPCS. *Ethnic minority populations in Great Britain. Pop trends*. London: HMSO, winter 1986 46

14 West Midlands Regional Health Authority. *Ethnic minorities in the West Midlands Health Region: locations*. January 1984:8, 63.

15 OPCS. *Population projections (area) 1983–2001*. London HMSO, 1986:6:3.

16 Tunstall-Pedoe H, Clayton D, Morris JN, Brigden W, McDonald L. Coronary heart attacks in East London *Lancet* 1975,ii:833–8.

17 Donaldson LT, Taylor JB. Patterns of Asian and non-Asian morbidity in hospitals. *BMJ* 1983,286·949–51

18 Balarajan R, Bulusu L, Adelstein AM, Shukla V Patterns of mortality among migrants to England and Wales from the Indian subcontinent. *BMJ* 1984;289 1185–7

19 McKeigue PM, Marmot MG, Adelstein AM, *et al* Diet and risk factors for coronary heart disease in Asians in Northwest London. *Lancet* 1985,ii·1086–90.

20 Lowry PJ, Glover DR, Mace PJE, Littler WA Coronary artery disease in Asians in Birmingham. *Br Heart J* 1984;52·610–3

21 Sewdarsen M, Jialal I. Coronary heart disease in Indians overseas [Letter] *Lancet* 1986,ii 159.

22 Mather HM, Keen H The Southall Diabetes Survey prevalence of known diabetes in Asians and Europeans. *BMJ* 1985;291 1081–4.

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CASE REPORT

Percutaneous laser valvotomy with balloon dilatation of the pulmonary valve as primary treatment for pulmonary atresia

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Abstract

A neonate with pulmonary atresia and an intact ventricular septum with a tripartite right ventricle was successfully treated by percutaneous balloon dilatation of the pulmonary valve. This was facilitated by previous laser valvotomy with a hot tip Trimedyne laser wire. There were no major complications. Four weeks later the patient was discharged home on no medication with peripheral oxygen saturations of 70% in air.

The management of patients with pulmonary atresia and an intact ventricular septum depends upon individual cardiac anatomy. In patients with a tripartite right ventricle and confluent pulmonary arteries, pulmonary valvotomy is usually favoured.[1] This has the advantages of decompressing the right ventricle (which is usually at suprasystemic pressure) and at the same time permitting anterograde flow into the pulmonary trunk, thereby promoting symmetrical growth of the pulmonary arteries. It has been suggested that laser valvotomy might offer an alternative to surgical pulmonary valvotomy.[2]

We report our experience with percutaneous balloon dilatation of an imperforate, dysplastic, pulmonary valve after initial laser valvotomy in a neonate with pulmonary atresia and an intact ventricular septum.

Case report

A male neonate (34 weeks' gestation and 2·2 kg) was investigated at 3 weeks of age because of central cyanosis. Cross sectional echocardiography showed pulmonary atresia with an intact ventricular septum. The pulmonary trunk measured 7 mm in diameter; the pulmonary arteries were confluent and a similar size. The pulmonary valve was dysplastic and imperforate. The right ventricle was tripartite. Colour flow mapping confirmed that the pulmonary circulation was dependent on flow through the ductus arteriosus. There was tricuspid regurgitation and the right ventricular systolic pressure was estimated to be suprasystemic. He was ventilated and treatment with intravenous prostaglandin E_2 was started. Cardiac catheterisation was performed from the left femoral vein. Initial right and left ventricular angiograms performed in a right anterior oblique projection confirmed the echocardiographic findings. The atretic pulmonary valve was clearly identified (fig 1). The coronary artery anatomy seemed normal.

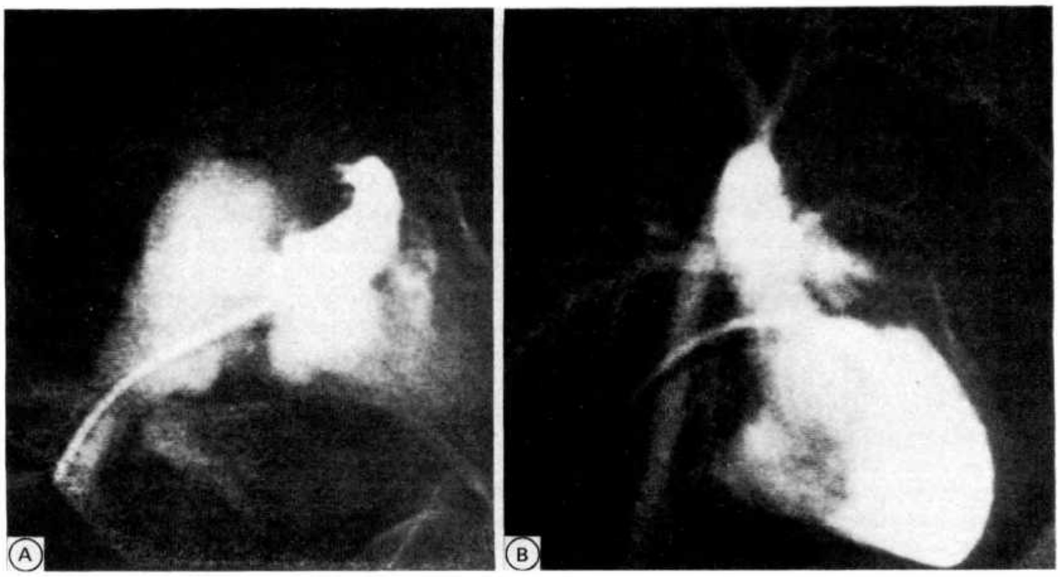

Figure 1 Initial (A) right ventricular and (B) left ventricular angiograms taken in a right anterior oblique projection showing pulmonary atresia with a blind ending infundibulum and good sized confluent pulmonary arteries supplied by the ductus arteriosus.

A size 4 French cobra catheter was manipulated into the blind ending infundibulum. A series of angiograms, taken in several different projections, were performed to ensure that the catheter was in a stable and suitable position, pointing posteriorly in line with the pulmonary trunk. Once this position was established a 0·018 inch Trimedyne floppy laser wire with a hot tip was passed through the catheter until it came in contact with the atretic pulmonary valve. The wire was connected to a Nd-Yag laser. Two bursts, each lasting two seconds, providing 3 W continuous wave laser energy proved sufficient to enable the wire to pass through the valve. The wire was kept in continuous motion with short to and fro movements in order to prevent it fusing with the delivery catheter or the intima of the pulmonary artery. The wire was then positioned in the distal right pulmonary artery without complication. We then attempted to advance the 4 French cobra catheter along the laser wire, across the pulmonary valve, and into the right pulmonary artery. Because this was not possible, an attempt was made with a 3 mm diameter coronary artery balloon catheter; however, this also proved unsuccessful. A 5 French cobra catheter was then repositioned within the infundibulum. A 0·014 inch high torque coronary angioplasty guide wire was advanced across the pulmonary valve through the passage created by the laser guide wire. The wire was then manipulated into a stable position within the distal left pulmonary artery. A 2 mm diameter coronary balloon catheter was then successfully positioned across the pulmonary valve and inflated twice. The procedure was repeated with a 5 mm diameter balloon catheter. Further dilatation with a larger balloon was not attempted because of recurrent episodes of supraventricular tachycardia and blood loss, estimated at approximately 50 ml. At the end of the procedure the systolic right ventricular pressure had fallen from 115 mm Hg to 74 mm Hg. A right ventricular angiogram was repeated. This showed anterograde flow into the pulmonary arteries and confirmed that there was no extravasation of contrast outside the heart (fig 2).

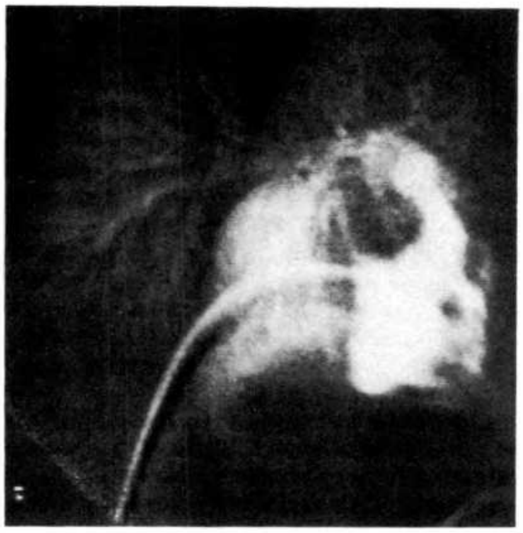

Figure 2 Right ventricular angiogram after laser valvotomy and balloon dilatation clearly showing anterograde filling of the pulmonary arteries.

Treatment with intravenous prostaglandin E_2 was continued for three weeks. He then underwent repeat balloon dilatation of the pulmonary valve and right ventricular outflow tract with a 7 mm diameter balloon catheter. One week later, after treatment with prostaglandin E_2 was stopped, the ductus arteriosus closed. His peripheral oxygen saturation in air was 70% and the estimated Doppler gradient across the pulmonary valve was 40 mm Hg. He was discharged home.

Discussion

The current management for patients with pulmonary atresia and an intact ventricular septum with a tripartite right ventricle and confluent pulmonary arteries is surgical pulmonary valvotomy. Many centres then continue intravenous prostaglandin E_2 to prevent the ductus arteriosus from closing to allow time for right ventricular compliance to fall. Subsequently, if there is still inadequate anterograde pulmonary flow, then an aortopulmonary shunt is usually created.[1] Neonates with critical pulmonary stenosis very often have similar haemodynamic and anatomical features. A similar surgical approach has been used in the past to treat these patients. More recently, however, this group of patients has been treated successfully with percutaneous balloon dilatation.[3]

Interventional cardiac catheterisation techniques have until recently been unhelpful in the treatment of patients with pulmonary atresia because there has been no reliable way of crossing the atretic pulmonary valve. Our report shows that this is possible with laser energy delivered by a hot tip quartz fibre wire. The use of laser techniques to treat patients with peripheral vascular disease[4] and coronary artery disease[5] is well reported. Fibreoptic "wires" are manipulated through guiding catheters to the site of arterial obstruction. A laser beam is then either focused directly on to the atheromatous lesion itself, or else is focused on to a metal tip of a laser wire, which heats up and delivers sufficient thermal energy to vaporise the obstruction. The advantages of the latter method is that there is greater control and the risk of perforation is less. We, therefore, adapted this method and in the event it proved relatively straightforward to cross the patient's pulmonary valve.

We recommend that laser valvotomy should be attempted only when a satisfactory catheter position within the infundibulum can be demonstrated. It was also important that the laser wire was kept moving during delivery of the pulses of laser energy because previous experience has shown that it is possible to fuse the wire with the intima of the artery or else perforate the guiding catheter. We found cross sectional echocardiography unhelpful as a means of confirming that the laser wire was in the correct position within the pulmonary artery. We therefore depended upon *x* ray screening in several different projections.

Although the initial laser valvotomy and the positioning of the laser wire into the pulmonary artery proved straightforward we experienced some difficulty in getting a catheter to advance along the wire and cross the pulmonary valve. The principal reason was that the floppy distal part of the laser wire, which was 40 cm long, did not provide sufficient support to enable the catheter to pass through the laser valvotomy channel. Potential solutions to this problem would be either to manipulate the laser wire through the ductus arteriosus and well into the descending aorta (which we were unable to do) thereby leaving the stiff portion of the wire across the valve or to manufacture a laser wire with a shorter floppy tip. Improvements to the taper of the catheter tip may also be helpful. Using the methods described we were able to perform the technique without major complication or morbidity. The procedure times and screening times were long; but this was an unfamiliar technique performed for the first time. Further experience should lead to a reduction in these times. The immediate result in our patient was comparable to that achievable with surgical pulmonary valvotomy, and accords with the early experience with laser valvotomy reported from Guy's Hospital.[2] The long term results clearly require further evaluation. Laser valvotomy combined with percutaneous balloon dilatation of the pulmonary valve, therefore, offers great potential in the treatment of patients with pulmonary atresia.

1 Anderson RH, Macartney FJ, Shinebourne EA, Tynan M *Paediatric cardiology*. Edinburgh: Churchill Livingstone, 1987·718–9
2 Qureshi SA, Rosenthal E, Tynan M, Anjos R, Baker E. Transcatheter laser assisted pulmonic valve dilatation in pulmonic valve atresia. *Am J Cardiol* 1991;67 428–31
3 Ladusans EJ, Qureshi SA, Parsons JM, Arab S, Baker EJ, Tynan M Balloon dilatation of critical stenosis of the pulmonary valve in neonates. *Br Heart J* 1990;63:362–7.
4 Sanborn TA, Cumberland DC, Greenfield AJ, Welsh CL, Guben JK. Percutaneous laser thermal angioplasty· initial results and 1 year follow up in 129 femoro-popliteal lesions. *Radiology* 1988;168 121–5
5 Linnemeier TJ, Cumberland DC. Percutaneous laser coronary angioplasty without balloon angioplasty. *Lancet* 1989,i:154–5.

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Proceedings of the British Cardiac Society

THE 70TH ANNUAL GENERAL MEETING of the British Cardiac Society was held at the Scottish Exhibition and Conference Centre, Glasgow on 30 April to 3 May 1991.

The President, D Chamberlain, took the Chair during private business. A McLeod and D Ward (on the retirement of S Hunter and I Hutton) and R Hall (on the retirement of A Henderson) were elected to Council.

Deaths during the year:
T E Lowe, J Kempson Maddox, J H Wright.

New Members 1991:
M Baig (Leeds); N Banner (Harefield); P Barnes (Salford); H Bethell (Hants); M Buchalter (Cambridge); N Buller (London); V Challenor (Southampton); J Chambers (London); A Coats (Oxford); T Cripps (Oxford); P Cummins (Birmingham); S Davies (London); K Evans (Swansea); A Fairfax (Stafford); A Fitzpatrick (Southampton); D Hackett (London); M Heber (Telford); K Hogg (Glasgow); S Holmberg (London); A Jones (Salisbury); C Jones (Cardiff); N Jowett (Pembrokeshire); C Kirk (Cardiff); S Large (Cambridge); R Levy (Manchester); N Lewis (Cardiff); P Lewis (Stockport); R Lewis (Yorkshire); J Lyons (Surrey); A McCance (Leicester); J McEwan (London); J McMurray (Glasgow); J Martin (London); R Maxwell (Gwynedd); W Morrison (Liverpool); D Mulcahy (London); M Papouchado (Bristol); J Parsons (Leeds); C Pattison (London); S Pocock (London); W Pugsley (London); P Quigley (Dublin); A Redington (London); S Richardson (Belfast); M Rigby (London); D Sandler (Derbyshire); D Smith (London); J Smith (London); T Spyt (Leicester); N Sreeram (Liverpool); P Sutton (London); P Thomas (London); P Wilmshurst (London); K Woods (Leicester).

New Corresponding Members:
R Falk (USA); H Madiera (Portugal); S Mody (India).

The following are abstracts of the papers that were presented.

Medical audit in the coronary care unit

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Systematic medical audit to assess and improve the quality of care has become an established part of routine clinical practice. In many departments this has relied on the examination of case records drawn at random from those of recent inpatients. The incomplete nature of this system gives no information on overall patient management strategies in an acute specialty such as cardiology. To monitor aspects of patient management within a coronary care unit (CCU) a tailor made, computerised system has been introduced, allowing the rapid collation of information for monthly, quarterly, and yearly audit. All patients admitted to the CCU have a form attached to their records on which details of their age, sex, diagnosis, drug treatment and other management, investigations, complications, and outcome are recorded. Forms are updated on the daily CCU ward round and on discharge from the unit. Information is coded and entered into a specially constructed computer database. Statistics are compiled by an audit program, written in dBASE programming language, to produce monthly and quarterly reports. These provide a breakdown of age distribution, length of stay, drug treatment, and outcome within diagnostic categories. The data are automatically formatted to produce an output that can be directly displayed at monthly clinical audit meetings without the need for further intervention or modification. Case notes relating to any deaths or complications are retained for discussion. During the first nine months of operation 492 patients were treated in the CCU and their details entered into the database. The resulting output provided an accurate picture of our acute cardiac management and led to a number of changes in management policy.

This system represents a straightforward and inexpensive approach to a more complete medical audit without imposing a large time burden on medical staff. It would be applicable to any unit and could be extended to cover any other areas of inpatient care.

Is the time saved by thrombolysis in accident and emergency departments significant?

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Royal Victoria Infirmary and Freeman Hospital,
Newcastle upon Tyne

The earlier thrombolysis is administered after myocardial infarction the greater the reduction in mortality. From July 1989 to November 1990 thrombolysis was administered to 264 patients with prehospital onset of acute myocardial infarction, 160 at the Royal Victoria Infirmary (RVI), where patients are admitted to the coronary care unit (CCU) from an accident and emergency department, and 104 at Freeman Hospital (FH), where patients are admitted directly to the CCU as there is no accident and emergency department. The catchment areas of these hospitals are similar. Time (minutes) from onset of pain to arrival in hospital was shorter in the RVI than in FH (145 *v* 193; $p < 0\cdot0001$). Time from arrival to thrombolysis was longer in the RVI than in FH (84 *v* 52; $p < 0\cdot0001$). Thus the time from onset of pain to thrombolysis in each hospital (RVI = 228, FH = 243; $p = 0\cdot09$) was similar. In the RVI thrombolysis was given in the accident and emergency department to 39 patients and in the CCU to 121 patients. In the accident and emergency department thrombolysis was given earlier after the onset of pain (176 *v* 245; $p = 0\cdot0008$) and earlier after arrival in hospital (49 *v* 96; $p < 0\cdot0001$) than in the CCU. Patients treated at the RVI's accident and emergency department were compared with patients treated at FH. After arrival in hospital the delay in receiving thrombolysis was the same in both groups, but administration of thrombolysis was sooner after the onset of pain in the RVI's accident and emergency department (176 *v* 243; $p = 0·0004$).

Provision of thrombolysis in an accident and emergency department can allow a subgroup of patients to receive thrombolysis almost 50 minutes sooner than after transfer to a CCU. Even direct admissions by a general practitioner to a CCU are associated with delay in receiving thrombolysis, which might be avoided by direct patient access to an accident and emergency department with facility for thrombolytic administration.

Thrombolysis at home: a dream became reality in the south of Italy

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Department of Cardiology, University of Rome; Catania; Vibo Valentia

We describe a programme of thrombolysis at home that is running in the south of Italy. The programme started in March 1990 with the purpose of treating patients with suspected acute myocardial infarction at home with thrombolytic treatment. The organisation consists of 364 local doctors trained in thrombolysis who administer the drugs at home; 25 cardiologists from our coronary care unit; a system of on line electrocardiographic transmission; and two ambulances equipped with resuscitation equipment. The doctors administer the thrombolytic agent after transmission of the electrocardiogram and consultation with the coronary care unit team. If the diagnosis of suspected acute myocardial infarction is confirmed by the cardiologists from the coronary care unit the ambulance leaves the hospital with an emergency team composed of two paramedical staff and a cardiologist. The programme aims at treating patients from a general population of 400 000 people. The thrombolytic drug administered is recombinant tissue-type plasminogen activator. Fifty three patients with suspected acute myocardial infarction have been treated so far. The diagnosis of acute myocardial infarction was confirmed in 21 of the 53 patients by electrocardiographic and enzymatic changes. The average time elapsed from the onset of symptoms and thrombolysis was 33·8 (25) minutes, and the average time from thrombolysis to admission to the coronary care unit was 75·6 (21·7) minutes. No deaths and no major bleeding complications were registered in the 53 patients treated. Twenty three patients had non-Q wave myocardial infarction and three required emergency coronary artery surgery. Although we have treated a small number of patients, we found the administration of the thrombolytic drug safe enough to continue giving it at home.

Clinical audit increases thrombolysis prescription rates to elderly patients with suspected acute myocardial infarction

T J Hendra, A J Marshall
Derriford Hospital, Plymouth

Fears of haemorrhagic complications, and doubts about efficacy, may limit thrombolysis prescription to elderly patients with suspected acute myocardial infarction. Retrospective five month audit of 264 patients aged > 64 admitted to the coronary care unit (CCU) found that 110 (42%) had acute myocardial infarction, of whom 13 (12%) received streptokinase, and 32 (35%) had such treatment withheld either because of dyspepsia or for unsatisfactory reasons. CCU staff were informed of this low thrombolysis uptake rate and nursing staff were instructed to question senior house officers when thrombolytic treatment was not prescribed for patients with chest pain. One year later a second, prospective five month audit was performed without the knowledge of CCU staff. During the second audit 55 out of 119 (46%) patients with acute myocardial infarction received either streptokinase or recombinant tissue-type plasminogen activator ($p < 0·01$ compared with first audit) and 13 out of 79 (16%) patients with unstable angina also received thrombolytic treatment. Reasons for omitting treatment were significantly different between the two studies ($p < 0·02$ by χ^2 test). Similar numbers of patients in both the first and second audits were excluded because of specific contraindications (20 (22%) *v* 17 (26%)), delay in presentation after onset of chest pain (14 (15%) *v* 18 (28%)), and delay in diagnosing acute myocardial infarction (25 (28%) *v* 23 (36%)). More patients were excluded because of dyspepsia (10 (11%) *v* 1 (2%)) or for unstated reasons (22 (24%) *v* 5 (8%)) in the first compared with the second audit.

The audit process has identified an easily remediable deficiency in the clinical management of elderly patients with acute myocardial infarction and has resulted in an improved thrombolysis uptake rate which is now similar to that reported in younger patients.

Audit of extended ambulance aid in management of cardiac arrest

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Ambulance crews receiving extended training learn the skills of vein cannulation, endotracheal intubation, drug administration, arrhythmia recognition, and defibrillation. We present a retrospective analysis of 274 report forms and electrocardiograph rhythm strips related to the management of out of hospital cardiac arrest by ambulance staff with these skills. Seven (2·5%) patients were managed for primary respiratory arrest; three were later discharged from hospital alive. In 98 (35·8%) patients the initial resuscitation protocol was for ventricular fibrillation (VF); 26 were admitted and 17 discharged. In 169 (61·7%) patients the initial resuscitation protocol was for asystole or electromechanical dissociation (EMD); 11 were admitted and one was discharged. Endotracheal intubation was attempted in 226 cases and was successful in 214 (94·7%). Vein cannulation was attempted in 219 cases and was successful in 192 (87·7%). Drugs were administered to 71 patients presenting in VF and to 145 patients in asystole or EMD. We judged that drugs were important in restoring cardiac output in four of the 17 survivors of VF and in the patient who survived EMD. Ninty seven per cent of drug administrations were non-contributory. There were deviations from the VF protocol in 27 (27·5%) cases: 11 related to incorrect energy of the first shock, 13 to incorrect timing of drug administration, and three to inappropriate drug usage. There were 27 (16·0%) deviations from the asystole protocol. The majority related to failure to complete the protocol and there were four cases of inappropriate drug use.

This study shows the need for continuing medical audit of paramedical practice.

Financial audit of antitachycardia pacing in patients with supraventricular tachycardia

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Freeman Hospital, Newcastle upon Tyne

This study assessed the financial implications of antitachycardia pacing in patients with frequent supraventricular tachycardia. Intertach pacemakers were implanted in 24 patients (mean age 46 years, five males): 21 had atrioventricular nodal re-entry tachycardia. A mean of 4·9 (range 0–8) drugs had failed and patients had been admitted to hospital a mean of 3·29 (0–31) times over a mean symptomatic period of 12·3 years (2 months to 25 years). The mean admission time for implantation was 2·8 (2–7) days. One patient with the Wolff-Parkinson-White syndrome underwent surgery. Over a mean follow up period of 21 (2–42) months all patients had their symptoms well controlled. Infection occurred in two patients and pain over the pacemaker required resiting in two. Two patients were admitted for supraventricular tachycardia. Six patients continue to take antiarrhythmic drugs. Costs were calculated, including value added tax, capital charges, and allocated overheads. The cost per year before pacing was £605 including drug costs (£163), clinic visits (£139), and hospital admissions (£303). The mean cost of pacemaker implantation was £3379, including the pacemaker and lead (£2839), admission and procedure (£369), readmissions (£136), and first pacing check (£35). Subsequent annual follow up cost was £74, including annual clinic visits (£35) and drug costs (£39). The cost of pacing is £3823 while medical management costs £3630, assuming pacemaker life of six years: with a 10 year life the cost is £4219 compared with £6050.

To conclude, the excess cost of implantation of an antitachycardia pacemaker is minimal in patients with frequent supraventricular tachycardia despite drug treatment and is justified by excellent control of symptoms and reduction of drug usage and hospital admissions.

Balloon dilatation of pulmonary valve for palliation of tetralogy of Fallot

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We attempted balloon dilatation of the pulmonary valve (BV) for palliation of recurrent cyanotic spells or severe persistent cyanosis in 67 patients with tetralogy of Fallot. Eight patients had associated complete atrioventricular septal defects. The median age at BV was 5 months (range 0·03–52 months) and the balloon to annulus ratio was 1·5 (range 0·86–3·44). There were no deaths resulting from BV. In three patients the pulmonary valve could not be crossed and an aortopulmonary shunt was performed at the same hospital admission. In the remaining 64 patients the systemic arterial oxygen saturation (SaO_2) after BV increased from 74% (range 44–99%) to 90·5% (range 45–100%); $p < 0·01$. Follow up catheterisation and angiography were performed in 35 patients 12 months (range 3–30 months) after BV. Of these, the condition of 24 had been adequately palliated by BV (group A), while 11 had required an aortopulmonary shunt 1 month (range 0–3 months) after BV (group B). The two groups were similar ($p > 0·1$) with respect to age at BV, pulmonary annulus diameter (AD), ratio of combined pulmonary artery to descending aortic diameter (PA:DAO) before BV, and the interval to follow up investigation. Patients in group A, however, had an immediate improvement in SaO_2 from 74% (range 56–99%) to 91% (range 69–100%) ($p < 0·01$). The change in SaO_2 in group B was non-significant from a median of 67% (range 47–83%) to 76% (range 45–97%). The AD in group A had increased from 6·75 mm (range 3·64–14 mm) to 10·55 mm (range 6·0–26·8 mm) ($p < 0·01$) and was greater than that expected from growth alone ($p < 0·01$) over the same period. The change in AD in group B was similar ($p > 0·1$) to that expected from growth alone over the period of follow up. The increase in PA:DAO was similar in both groups from a median of 1·85 to 2·21 in group A and from 1·67 to 2 26 in group B ($p > 0·1$). Of 42 patients who had corrective surgery, 27 required a transannular patch for reconstruction of the right ventricular outflow tract. The use of a transannular patch was similar in groups A and B.

BV is safe, provides adequate palliation, and promotes growth of the annulus and pulmonary arteries in tetralogy of Fallot. Failure to improve SaO_2 immediately after BV is an indication for an aortopulmonary shunt.

Mechanisms of relief of right ventricular outflow obstruction by percutaneous balloon dilatation in tetralogy of Fallot

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Twelve children with tetralogy of Fallot and increasing cyanosis underwent ballon dilatation of the right ventricular outflow tract (RVOT) as their only palliative procedure. Mean age at the time of the first dilatation was 10·5 months (range 5·5 to 20 months). Four children subsequently underwent a second balloon dilatation 3·5 to 10 months (mean 3 months) after the first procedure. There were no major complications during any of the dilatation procedures, and all the children experienced an inprovement in arterial oxygen saturations. The time interval between the first dilatation and total correction was 3 to 19 months (mean 9·4 months). At the time of surgery tearing of a pulmonary valve cusp was noted in five patients—but in none was there any evidence of annular disruption. In eight children there was extensive scarring of the infundibulum consistent with muscular disruption at the time of RVOT dilatation, with subsequent fibrosis and contracture of the RVOT. This may have contributed to later recurrence of the RVOT obstruction but did not preclude a satisfactory surgical repair. Signs of balloon dilatation were absent in only one child.

Balloon dilatation of the RVOT relieves symptoms for a variable length of time and is a suitable alternative primary palliative procedure in children with symptoms of tetralogy of Fallot.

Five year follow up after balloon dilatation of pulmonary valve: is obstruction completely relieved at the expense of pulmonary incompetence?

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No long term data exist after balloon dilatation of the pulmonary valve (BPV). We reviewed 34 of our first 40 consecutive patients a mean of 5·2 (SD 0·8) years after BPV. Twenty seven had isolated pulmonary stenosis, five Noonan's syndrome, and two previous surgical valvotomy. Six patients were excluded because of death (two), residence abroad (two), pulmonary artery stenoses (one), and Ebstein's anomaly (one). The transpulmonary gradient was 73 (34) mm Hg before BPV, 34 (26) immediately after, 22 (9) at catheterisation 6 (0·6) months later (29 patients), and 19 (10) by Doppler ultrasonography at five years. Repeat BPV had been performed in eight patients (three with Noonan's syndrome), which was the index procedure for analysis. All had symptoms. At five years eight patients (four with Noonan's syndrome) had a residual transpulmonary gradient >20 mm Hg (group A) whereas in the remaining 26 the transpulmonary gradient was <20 mm Hg (group B). In the seven patients with Noonan's syndrome and in patients with previous surgical valvotomy transpulmonary gradient was reduced from 74 (24) before BPV to 23 (12) at five years, with the highest residual gradient being 41 mm Hg. The balloon to annulus ratio was larger for patients with pulmonary stenosis in group B than in group A (1·2 (0·1) *v* 1·0 (0·07), $p = 0{\cdot}005$), whereas large balloons were used in patients with Noonan's syndrome in group A (1·3 (0·1)). Patients in group B were more likely to have significant pulmonary incompetence (6/24 *v* 0/8) and had a greater right ventricular to left ventricular long axis diastolic dimension ratio (0·47 (0·1) *v* 0·35 (0·04), $p = 0{\cdot}05$). Pansystolic tricuspid regurgitation on Doppler ultrasonography was found in only two patients. Relief of transpulmonary gradient persisted at five years especially when "oversized" balloons were used. Acceptable results can still be obtained for dysplastic valves. More complete relief of transpulmonary gradient was associated with increased RV dimension probably because more pulmonary incompetence is induced. This is well tolerated at five years but may be important in the longer term.

Early results of transcatheter laser assisted balloon dilatation of pulmonary valve atresia

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Transcatheter laser assisted balloon dilatation for pulmonary valve atresia was attempted in seven children aged 1 day to 2 years (weight 2·1–9·1 kg). In five the ventricular septum was intact but in two there was also a ventricular septal defect. Blalock-Taussig shunts had been performed in three, while in four the arterial duct was still patent. A 0·018 inch "hot tip" laser guide wire, powered by a 3·5 Watt Nd-YAG laser, successfully crossed the atretic valve in six patients: in four antegradely from the right ventricle and in two retrogradely from the pulmonary artery. Balloon dilatation of the pulmonary valve was then performed with 5–8 mm balloons. In one patient with additional infundibular atresia the laser wire perforated the right ventricle during antegrade advancement; the resulting cardiac tamponade responded to needle pericardiocentesis and the leak had sealed at operation for a shunt three hours later. During follow up at 2–8 months oxygen saturations $>85\%$ were maintained in all but one (72%) and none required surgery. Doppler pulmonary valve gradients ranged from 18 to 75 mm Hg, and of those with an intact septum, the arterial duct had closed in two and the septal defect had either closed or become restrictive in all.

Laser assisted pulmonary valve dilatation is a promising new treatment strategy in patients with pulmonary valve atresia. Its potential role in avoiding palliative surgical shunting and right ventricular outflow tract reconstruction will be determined during longer term follow up.

Balloon dilatation of aortic recoarctation: determinants of haemodynamic results

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Balloon dilatation of recoarctation of the aorta was performed in 26 patients who underwent 30 procedures over eight years. Age at first dilatation ranged from 2·6 months to 18·3 years (median 8 months). After dilatation the systolic gradient decreased from 49 (17) mm Hg to 20 (17) mm Hg ($p < 0{\cdot}001$). The gradient was <20 mm Hg after the first dilatation in 17/26 (65%) patients. In the remaining nine patients gradients of 25–80 mm Hg remained. During follow up of 2 months to 6·7 years (mean 1·8 years) five of the 17 patients with good initial results developed further restenosis needing repeat dilatation or surgery (one for an aneurysm). Of the nine patients with gradients >20 mm Hg, one had repeat dilatation and three reoperation; five were managed conservatively. After follow up of 2 months to 6·7 years (mean 1·8 years) 15 (58%) patients had a good and 11 (42%) a poor late result. Two (8%) patients developed aneurysms, one early and one 2 months after balloon dilatation. The aortic diameters at different levels of aortic arch and isthmus, normalised to aortic diameter at diaphragm level, in patients with good results were significantly larger than those in patients with poor results. A balloon to aortic diameter ratio at diaphragm level close to 1·0:1·0 had a significantly favourable influence on late results; ratios of $<0{\cdot}8{:}1{\cdot}0$ were associated with a poor outcome, both early and late.

Balloon dilatation, though a preferable alternative to surgery, occasionally fails to produce a good result. This is influenced both by the anatomy of the aortic arch and by the balloon to aortic ratio at diaphragm level.

Assessment of suitability of atrial septal defects for transcatheter closure in children: role for transoesophageal echocardiography?

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The ability of transoesophageal echocardiography to identify the features of oval fossa atrial septal defects that determine suitability for transcatheter closure was assessed in a prospective study. The features considered were size, fenestration, adequacy of margin for anchorage of the device, and clearance from right pulmonary veins, coronary sinus, inferior caval vein, and mitral valve. Findings were compared with operative anatomy and precordial echocardiography. Transoesophageal echocardiography with a 5 MHz, 13 mm single plane oesophageal transducer was performed in 12 anaesthetised children before surgery.

Age and weight at study ranged from 3 to 9 years (median 5) and from 13 to 23 kg (median 17). All studies took less than 10 minutes and were uncomplicated. One defect had multiple fenestrations, not identified on precordial echocardiography. Direct measurement of the horizontal size of the defect was possible and estimation of vertical size was attempted by noting movement of the endoscope at the teeth while the defect was scanned from its superior to inferior margins. In all cases distances from the defect to the posterior atrial wall and to the mitral valve could be measured. The coronary sinus was seen in four patients. The caval veins and pulmonary venous inflow were identified in all patients but not in the same echo plane as the defect. In one case proximity to the inferior caval vein, which would have precluded clam shell closure was not appreciated. The exact site of entry of the right upper pulmonary vein was rarely established.

Transoesophageal echocardiography provides some anatomical detail not readily available from precordial echocardiography, estimation of adequacy of margin around the defect for anchorage of an occluding device and clearance from the mitral valve. It cannot, however, reliably identify all the features which determine suitability for transcatheter closure such as vertical size and the proximity of the right pulmonary veins, coronary sinus, and inferior caval vein, which are not imaged in the same plane as the defect.

Angioplasty of total occlusions by the Magnarail system

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Percutaneous transluminal angioplasty (PTCA) of coronary occlusions has produced disappointing results, with a reported primary success rate of between 42% and 66% compared with over 95% in non-occlusive stenoses. The Magnarail system (Schneider) may possess advantages to improve results. The 0·021 inch guide wire has a steel shaft over which balloons of differing diameters may be passed. At the tip of the wire is a flexible tungsten spring and a 1 mm olive. This arrangement maximises "pushability" and minimises intimal trauma. We investigated the success rate in 54 patients with coronary occlusions (left anterior descending in 12, right coronary artery in 25, circumflex in 14, vein grafts in three). The index vessel was considered to be occluded in all cases. There was angiographic evidence of bridging collaterals in 14 patients, retrograde collaterals in 33, and both in five. Twelve vessels had no distal flow. There were no deaths and no patients required surgery. The primary success rate (a residual stenosis of less than 50% and disappearance of collaterals when present) was 83·0%. The age of the occlusion could be estimated from a change in anginal severity or myocardial infarction. In 32 patients it was estimated to be less than three months (group A) and in 22 greater than three months (group B). The primary success rate in group A was 84·0% and in group B 82·0% (NS). The commonest reason for failure was intraprocedural occlusion in group A (5/5 failures) whereas in group B failure was either due to inability to cross the lesion (2/4 failures) or due to the wire tracking preferentially into a proximate side branch (2/4 failures). In 14 patients it was necessary to redilate the lesion with a different sized balloon. This was easily performed over the guide wire. A disadvantage of the system was the guide wire opacity which necessitated withdrawal before angiography. It was often possible to recross the lesion even if a dissection was present.

Thus the Magnarail system is highly successful in PTCA of coronary occlusions and has a primary success rate that approaches that of PTCA of non-occlusive stenoses. Comparisons with other equipment are required but it should be considered the system of first choice in angioplasty of total occlusions.

Treatment of chronic coronary artery occlusions with the Terumo glide wire

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Seventeen patients (12 male, five female) with coronary occlusions of more than three weeks duration (range 3 weeks–2 years) and lesions that could not be crossed with conventional or olive tipped wires (Magnum wire—three cases) were operated on with either the 0·35 (eight cases) or the 0·18 (nine cases) Radiofocus Terumo glide wire. The 0·35 wire was introduced into the coronary artery without a balloon catheter. If this wire crossed a lesion it was withdrawn and a conventional wire was introduced along the track made by the larger wire. The 0·18 wire was introduced via a large lumen coronary balloon. Coronary arteries treated were the right coronary in nine patients, the circumflex in three, and the left anterior descending in four. The 0·35 wire crossed in five out of eight cases. The 0·18 wire crossed in six out of nine cases. Angiography after angioplasty with the use of these wires showed some degree of dissection in all cases. The overall success in our institution in crossing occlusions with conventional wires is 41% in 80 cases, the use of hydrophilic wires in chronic coronary occlusions having increased the primary success rate of our procedures.

Further investigations of this technology may reduce the need for expensive devices for the treatment of coronary occlusions.

Myth of the "safe procedure": disobliteration of chronically occluded coronary arteries

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The risk of myocardial infarction and its complications should be lower in coronary angioplasty (PTCA) of chronically occluded vessels than it is in PTCA of non-occluded vessels. We reviewed the results of disobliteration of chronic coronary occlusions at our institution between 1987 and 1990. An attempt was made to recanalise 98 occluded vessels in 93 patients (left anterior descending artery in 46, left circumflex artery in 14, right coronary artery in 38). Primary success (defined as antegrade flow of contrast at the end of the procedure) was achieved in 47 vessels (47·9%). Failure to cross the occlusion, without adverse consequences, occurred in 41 lesions (41·8%). Local dissection of the vessel was observed in two cases (2%) and thrombus formation was seen in another two (2%). An extensive dissection of the target vessel (the right coronary artery in all cases) occurred in six patients (6 1%) and was associated with chest pain and the electrocardiographic changes of acute myocardial ischaemia in five (83·3%). In all cases chest pain was controlled medically (including laser balloon angioplasty in one and stent implantation in two), but there was myocardial necrosis in three. There was no change in symptom class in three patients, but the condition of three deteriorated by at least one class and all three patients underwent coronary artery bypass grafting, two during the same hospital admission.

PTCA of chronically occluded coronary arteries is associated with a low primary success rate. The risk of myocardial ischaemia and infarction is similar to that of PTCA in other settings, despite "support" for the distal vessel via collateral channels from the contralateral coronary artery. Disobliteration of the right coronary artery in particular carries a high risk of dissection (15·8%), for reasons which are not yet clear.

Impact of late restenosis in long term outcome of percutaneous transluminal coronary angioplasty for chronic total occlusions

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Though percutaneous transluminal coronary angioplasty (PTCA) can often recanalise chronically occluded vessels, controversy remains as to the clinical benefit of the procedure in the long term. We report on the follow up over a period of 20 (16) months of 72 patients who underwent PTCA for chronic total or functional occlusion. The primary success rate was 65%. The groups in whom PTCA was successful and unsuccessful were similar in terms of age, sex, cardiovascular history, and number of diseased vessels and vessels dilated. Of the 25 patients in whom PTCA was unsuccessful, eight (32%) were referred for coronary artery surgery (CAS) and 17 (68%) were treated medically. Of the group in whom the procedure was successful, 27 (57%) remained free of symptoms or had minimal symptoms throughout the follow up and 17 (36%) had recurrence of symptoms and underwent repeat angiography. All had restenosis of the previously occluded artery. Three patients were referred for CAS, 11 underwent repeat PTCA, and three continued with medical treatment. Repeat PTCA failed in four patients (success rate 73%). Three of them were referred for surgery. In addition, there were one cardiac and two non-cardiac deaths, all in the group in whom PTCA was successful. During the first six months of follow up CAS was indicated in eight (32%) patients in the group in whom PTCA failed while only three (6%) patients in the same group referred for surgery because of symptomatic restenosis with or without failed repeat PTCA ($p < 0·005$). Symptomatic restenosis occurred, however, in six patients after the first six months of follow up (35% of all symptomatic restenosis), resulting in three additional referrals for surgery and making the total figure of referrals for CAS in the successful group six (12%). At the end of follow up a significant difference in the number of patients without symptoms or with minimal symptoms in the successful and failed groups was found among survivers who did not undergo CAS (32/35 *v.* 9/16 respectively, $p < 0·03$).

We conclude that patients with successful PTCA of chronically occluded arteries benefit in the long term from a significant reduction in their anginal symptoms. Late symptomatic restenosis seems to be common, however, and is a cause of late referral for CAS, reducing the early advantage of successful over failed cases in terms of need for surgery.

Emergency treatment of acute coronary dissection during angioplasty

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Coronary artery dissection causing acute myocardial ischaemia complicates 5% of coronary angioplasty (PTCA) procedures. The outcome of emergency coronary artery bypass grafting (CABG) in this situation is frequently unsatisfactory because of delay in re-establishing coronary perfusion. To provide more immediate reperfusion we have used, in a non-randomised fashion, laser balloon angioplasty (LBA) or self expanding intracoronary stents in 44 patients in whom PTCA was complicated by coronary artery dissection. LBA was performed in 13 patients and stent implantation performed in 31. A satisfactory immediate result, with restoration of antegrade blood flow and resolution of clinical and electrocardiographic evidence of myocardial ischaemia, was obtained in 41 patients. In one patient stent implanatation was undertaken after an unsatisfactory result on LBA. Emergency CABG was performed in one patient after stent implantation. Seven patients (23%) receiving stent implantation had acute myocardial infarcts (one Q wave, six non-Q wave), one of whom died 24 hours after the procedure (3% mortality), and one patient receiving LBA had a Q wave myocardial infarct. Stent occlusion requiring disobliteration within the first week of implantation occurred in two patients (one received thrombolysis, the other repeat PTCA) and was associated with non-Q wave infarction in one patient. During six months of follow up restenosis occurred in four patients in the LBA group (29%) and was managed by repeat PTCA in two and CABG in two. In the group receiving stent implantation there was one clinically silent permanent occlusion and two deaths (1 week and 3 months after the procedure). Restenosis was seen in two patients (6·4%) in this group, one of whom underwent PTCA and the other CABG.

Both LBA and coronary stent implantation can ensure rapid coronary reperfusion with myocardial salvage in acute coronary dissection after PTCA and are acceptable alternatives to emergency CABG. LBA has fewer early complications, but stent implantation is associated with lower rates of restenosis.

Coronary angioplasty in 1990: experience of 100 procedures in a centre without on site surgical cover

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The debate on the need for on site surgical standby for coronary angioplasty is based on the currently accepted success rates of 90% and the need for emergency surgery of between 2% and 5%. Increased operator experience and technical advances might be expected to result in an improvement in these figures. We present the data on the first 100 procedures since 1 January 1990 performed in a centre without on site surgical cover. Coronary angioplasty was performed in 90 patients (71 male, age 58·5 years). The clinical indication was stable angina in 60 patients, unstable angina in 25, postinfarction unstable angina in 13, and acute myocardial infarction in two. Single vessel angioplasty was performed in 61 patients, two vessel in 38, and three vessel in one and 13 patients had total occlusions. The overall success rate was 91%, and 98·9% when total occlusions were excluded. There were no deaths or need for emergency bypass surgery. One patient sustained a Q wave myocardial infarction and one patient had an abrupt occlusion successfully redilated. Two patients were cardioverted for ventricular tachycardia during the procedure, one patient required ventilation for a pulmonary embolus 24 hours after the procedure, and three patients had complications related to arterial access. Restenosis requiring repeat angioplasty was required in nine patients.

These results in a patient population with a higher than average risk profile due to the high percentage with unstable and postinfarction angina suggest that the trend towards improved success in coronary angioplasty persists. None of the patients required emergency surgery, which questions the requirement for immediate on site surgical standby for all patients undergoing coronary angioplasty.

Assessment of cardiac valves by endovascular ultrasonography: a new approach

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Current methods of valve assessment are still not infrequently prone to interpretative error and a "gold standard" has yet to be found. We assessed intravascular ultrasonography in seven explanted bioprostheses mounted in a prototype valve rig approximating "normal" cardiac conditions and studied them with a 20 MHz mechanically rotating probe. This was compared with simultaneous video optical images. In five cases good correlation was obtained, including orifice area (with a calibrated grid), commisural anatomy, leaflet pliability, and tissue characterisation (calcification *v* fibrosis *v* normal). In all five cases the mode of valve failure was accurately assessed (critical stenosis, two cases; leaflet perforation or tear, or both, two; and subacute bacterial endocarditis, one). The maximum depth of field in our system was 10–12 mm. This resulted in far field attenuation with poor image quality in the remaining two valves, which were both large with peripheral tears.

We conclude that intravascular ultrasonography seems to provide definition of anatomy superior to conventional imaging systems. The prime use of the present system would be in evaluating valve stenosis, or small valves, because of its reduced depth of field. The ideal intravascular ultrasonography imaging system should utilise a lower frequency (10–15 MHz) or a larger aperture to extend the range and depth of field such that both large and small valves, whether incompetent or stenotic, could be usefully and accurately studied.

Edinburgh randomised trial comparing Björk-Shiley and porcine valve replacements: results at 12 years

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Patients undergoing heart valve replacement may receive a mechanical prosthesis necessitating lifelong anticoagulant treatment or a porcine bioprosthesis without an absolute need for anticoagulants. We carried out a randomised prospective trial to compare the durability and incidence of valve related complications of the Björk-Shiley mechanical prosthesis with the Hancock and Carpentier-Edwards porcine prostheses. The mitral valve was replaced in 261 patients, the aortic in 211, and both in 61; survivors were followed up for a mean of 12 years. We found a trend towards improved actuarial patient survival with the Björk-Shiley prosthesis, but this was not statistically different (Björk-Shiley 51·5% (3·2%), porcine 44·4% (3·2%) alive at 12 years; $p = 0{\cdot}08$, log rank test). There was no significant difference in the actuarial incidence of reoperation at five years, but at 12 years significantly more patients with a porcine prosthesis had undergone reoperation (Björk-Shiley 8·5% (2·0%), porcine 37·1% (4·1%); $p < 0{\cdot}001$). An analysis combining death and reoperation as end points for an actuarial assessment of survival with the original prosthesis intact confirmed improved valve survival in patients with Björk-Shiley prostheses (Björk-Shiley 48·6% (3·2%), porcine 30·0% (3·0%) at 12 years; $p < 0{\cdot}001$). Bleeding requiring admission to hospital or blood transfusion occurred significantly more frequently in those with Björk-Shiley prostheses (Björk-Shiley 18·6% (3·2%), porcine 7·1% (2·3%) at 12 years; $p < 0{\cdot}01$). There was no significant difference at 12 years in the actuarial occurrence of embolism (Björk-Shiley 21·1% (3·1%), porcine 26·4% (3·5%)) or endocarditis (Björk-Shiley 3·7% (1·4%), porcine 4·6% (1·6%)).

We conclude that there is improved valve survival with the Bjork-Shiley prosthesis but with an attendant increased risk of bleeding associated with the need for anticoagulant treatment.

Late functional results after surgical closure of acquired ventricular septal defect

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Between 1973 and 1988, 101 patients (mean age 69 years, range 53–88) underwent surgical treatment for acquired ventricular septal defect (VSD) in this unit, with an early mortality of 20·8%. Of the 60 current survivors, 58 (97%) were followed up for 38·8 (34) months and form the study population. Clinical examination, radionuclide multigated acquisition ventriculography, and colour flow mapping was undertaken in 46 patients, 42 of them having additional 24 hour Holter monitoring; the remaining 12 were interviewed by telephone. Subjective exercise tolerance was adequate for daily living in 47 patients (81%) (New York Heart Association class I, 29 patients; class II, 18 patients).

Left ventricular ejection fraction was reduced at 39% (15%) for the group. Colour flow mapping identified a small, haemodynamically insignificant residual VSD in eight patients (17%). Important, but asymptomatic arrhythmias were noted on a 24 hour tape in 28 patients (67%), including frequent monomorphic or polymorphic ventricular premature beats (17), ventricular tachycardia (two), paroxysmal atrial fibrillation (two), paroxysmal atrial tachycardia and supraventricular tachycardia, or both (seven). Exercise testing failed to provoke arrhythmias in any patient.

Despite significant impairment of ventricular function, the majority of survivors of surgical repair of acquired VSD can expect a good quality of life. Asymptomatic arrhythmias are common in the survivors of acquired VSD repair and may account for the late mortality in this group.

Overcoming peroperative spasm of the internal mammary artery: which is the best vasodilator?

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After mobilisation, vasospasm often reduces flow through the internal mammary artery. An established method of relaxing the artery and increasing flow is to wrap it in a papaverine soaked swab. To our knowledge, the ability of other topical vasodilators to overcome spasm of the internal mammary artery has not been studied clinically. We have investigated the effect of five agents: normal saline, papaverine, nifedipine, glyceryl trinitrate, and sodium nitroprusside on free flow in the artery in 50 patients undergoing myocardial revascularisation. Under controlled haemodynamic conditions free flow was measured before any pharmacological intervention and a median of 18·5 minutes after the pedicle had been sprayed with one of five agents. Normal saline produced a small increase in flow from a median of 23 (range 17–88) to 38 (20–84) ml/min (NS), whereas a significant increase occurred with papaverine from 25 (16–78) to 43 (34–112) ml/min ($p < 0{\cdot}01$). Nifedipine and glyceryl trinitrate raised free flow almost threefold, from 23 (14–66) to 71 (45–118) ml/min and from 23 (14–58) to 62 (46–126) ml/min respectively (both $p < 0{\cdot}001$). Sodium nitroprusside, however, with an increase in flow from 26 (10–58) to 108 (46–196) ml/min, 250% above control values, proved to be more effective than nifedipine and glyceryl trinitrate ($p < 0{\cdot}05$).

We therefore recommend the topical use of sodium nitroprusside to relieve peroperative spasm of the internal mammary artery.

Mechanisms underlying intimal thickening in arteriovenous bypass grafts

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In pig saphenous vein to carotid artery bypass grafts the time course of changes in the following variables were related: (*a*) medial and intimal size by morphometry of transverse sections, (*b*) cell number and density by DNA concentration and by counting nuclei in transverse sections, (*c*) endothelial morphology by scanning electron microscopy, and (*d*) tissue cholesterol concentration. In the first week after grafting medial and intimal thickening were associated with an increase in cell number. Between one and four weeks after grafting further rapid medial and intimal thickening occurred without a further increase in cell number but with a reduction in cell density, which suggested that cell migration, hypertrophy, and the laying down of extracellular matrix were responsible. Between four and 39 weeks after grafting a slower rate of medial and intimal thickening was associated with a parallel increase in cell number and no further change in cell density. A largely intact endothelium was observed in grafts recovered either one or four weeks after grafting. Cholesterol concentration was slightly raised one week after grafting but it declined to values similar to those in veins by 27 weeks after grafting.

We conclude that three processes contribute to medial and intimal thickening—namely, (*a*) an initial phase of rapid smooth muscle cell proliferation, (*b*) smooth muscle cell migration, hypertrophy, and synthesis of extracellular matrix, and (*c*) a late phase of slower smooth muscle cell proliferation. Late smooth muscle cell proliferation occurs under a morphologically intact endothelium and without progressive cholesterol accumulation.

Cardiac surgery: breaking with intensive care

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The need for intensive care units for the recovery of patients undergoing cardiac surgery is questionable on clinical and economic grounds. Between January and December 1990, 705 adult patients underwent open heart surgery at the Oxford Heart Centre. Six hundred and twenty five of these patients were managed postoperatively through a recovery area. This practice is based on a prospective study of 245 consecutive patients over the first four month period. The mean age of the patients was 63·2 years, and they underwent a wide variety of operative procedures. Ninety per cent of them underwent recovery in a dedicated three bedded recovery area where the management protocol led to rapid extubation and step down in dependency care. The median time for ventilatory support was 90 minutes after transfer to the area, with only five patients being subsequently admitted to the general intensive care unit for prolonged respiratory and cardiac support. During the same period only 10 patients were electively admitted to the general intensive care. Two patients (0·8%) in this group died in hospital.

Our study confirms that nearly 90% of patients undergoing cardiac surgery today may undergo recovery safely and effectively in a more economical area.

Contribution of systolic compression to impaired coronary reserve in cardiac hypertrophy

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The impaired coronary reserve associated with left ventricular hypertrophy may be due to a structural change in the coronary vasculature or to a functional impairment of flow secondary to increased extravascular forces. Left ventricular hypertrophy was induced in guinea pigs by aortic constriction. The vascular effects of hypertrophy were studied in isolated buffer perfused hearts 72 (6) days after aortic constriction (n = 15) and compared with sham operated controls (n = 12). Maximal dilatation and heart block were induced by adenosine infusion, allowing systolic effects to be abolished by brief cessation of pacing. Coronary reserve was defined as (vasodilated flow)/(basal flow) × 100%. Coronary resistance was computed from the pressure flow relation over the perfusion range 30–70 mm Hg. To examine the effects of systole on minimal coronary resistance an extravascular index was defined as the percentage increase in mean flow when systolic effects were eliminated. Basal flow, coronary reserve, and the extravascular index were measured at a perfusion pressure of 50 mm Hg. Heart weight was increased in the hypertrophied group (4·8 (0·2) g) compared with controls (3·3 (0·1) g) (p < 0·001). Basal coronary flow was equal in both groups (3·2 (0·2) *v* 3·0 (0·2) ml/min/g), but minimal coronary resistance was increased in the hypertrophied group (4·5 (0·44) *v* 3·70 (0·37) mm Hg/ml/min/g) (p < 0·05), giving rise to a decreased coronary reserve (141% (5·5) *v* 231% (24·1)) (p < 0·01). The minimal coronary resistance of the whole heart was equal in both groups (0·95 (0·1) *v* 1·06 (0·1) mm Hg/ml/min). The extravascular index was increased in the hypertrophied hearts (59·2% (3·5) *v* 45·7% (5·0)) (p < 0·05), despite there being no difference in left ventricular systolic or diastolic pressure at a constant heart rate (200 beats/min). Analysis of the pressure flow relation in the beating heart showed a greater increase in minimal coronary resistance induced by systole in the hypertrophied hearts (1·6 (0·2) *v* 0·9 (0·1) mm Hg/ml/min/g) (p < 0·05).

These findings indicate that coronary reserve is impaired in hypertrophied guinea pig hearts because of inadequate vascular development. In addition, systolic compression reduces coronary flow to a significantly greater extent in hypertrophied than normal hearts.

Membrane current changes as basis for arrhythmogenesis in hypertrophied myocardium

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In hypertrophied myocardium action potential duration (APD) is prolonged, and this may be a key to the substantially increased risk of arrhythmias in this condition. Using the voltage clamp technique we have investigated membrane currents in a model of chronic, stable left ventricular hypertrophy to find out which current mechanisms are involved in APD prolongation. Systemic pressure overload was induced by subrenal aortic coarctation in the guinea pig. Single cardiac myocytes were isolated by enzymatic perfusion, and on stimulation at 0·2 Hz the mean APD at 90% repolarisation (APD$_{90}$) was 310 (SEM 17) ms in cells from sham operated animals (n = 22) and 358 (13) ms in hypertrophied cells (n = 34, p < 0·05, unpaired *t* test). The density of the L type calcium current was significantly increased in hypertrophy (−11·1 (0·7) pA/pF, n = 34, compared with −8·6 (0·4) pA/pF in control myocytes, n = 25, p < 0·02). The current generated by sodium-calcium exchange was elicited by interrupting action potentials at different times and clamping to the resting potential. This current, which is also the principal component of the arrhythmogenic "transient inward" current, was greatly increased and prolonged in hypertrophied cells (current density −1·6 (0·2) pA/pF in controls, n = 7, −2·8 (0·2) pA/pF in hypertrophy, n = 23, p < 0·01). The time dependent potassium current, i$_k$, is not significantly different in hypertrophied cells. Increases in calcium and sodium-calcium exchange current therefore account for APD prolongation in hypertrophy.

In this model of hypertrophy not associated with heart failure we found an increase in cell contractility. Mean cell shortening on depolarisation was 8·4 (1·2) µm in control myocytes n = 15, 20·0 (1·8) µm in hypertrophied myocytes, n = 25, p < 0·001. The time to peak contraction is unchanged but the duration of contraction is prolonged in hypertrophy.

Diltiazem reduces left ventricle mass without increasing myocardial collagen concentration in deoxycorticosterone acetate-salt hypertension

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Some antihypertensive drugs reverse left ventricular hypertrophy but may increase the degree of myocardial fibrosis if concurrent collagen regression does not occur. Laboratory and clinical reports suggest that diltiazem can reverse left ventricular hypertrophy but little is known about its effects on collagen metabolism. This study examined the effects of short term diltiazem treatment on left ventricle mass and collagen content in a hypertensive rat model. Stable deoxycorticosterone acetate (DOCA)-salt hypertension was induced in male rats over 12 weeks. They were then divided into two groups. One group (n = 5) received diltiazem in distilled water as drinking fluid (0·3 mg/ml increased over two weeks to 0·7 mg/ml and maintained at 0·7 mg/ml for a further five weeks). The other group (n = 6) received distilled water. Normotensive controls received tap water throughout. After seven weeks hearts were removed and the dry mass of the left ventricle free wall plus interventricular septum was determined. Collagen content was estimated by spectrophotometric assay of hydroxyproline in the hydrolysed samples. There was an 18% reduction in systolic pressure in the diltiazem treated group (164 (5) mm Hg compared with 200 (5) mm Hg; p < 0·01). Although left ventricle mass was significantly higher in both hypertensive groups when compared with normotensive controls, absolute left ventricle mass was 18·5% lower in the treated group (p < 0·05). There was no significant difference between the hydroxyproline concentration in the hypertensive groups but total content of hydroxyproline in the treated group was 18·8% lower than in the untreated hypertensive group (p < 0·05).

Collagen regression appeared to parallel left ventricle mass reduction and there was no increase in the ratio of fibrotic tissue within the myocardium after regression of left ventricular hypertrophy with diltiazem. Thus it is likely that left ventricle mass reduction with diltiazem would not be associated with an unfavourable increase in myocardial stiffness.

Identification of α and β cardiac myosin heavy chain isoforms as major autoantigens in idiopathic dilated cardiomyopathy

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Immunisation with the cardiac myosin isoform induces experimental autoimmune heart disease in genetically predisposed mice. These mice produce heart specific autoantibodies, some of which are directed against the cardiac myosin isoform. We have reported the presence of circulating heart specific autoantibodies in a subgroup (25%) of patients with dilated cardiomyopathy (DCM) by indirect immunoflourescence. To identify the autoantigen(s) recognised by heart specific autoantibodies in human disease we tested by western blotting serum samples from 14 patients with DCM who were positive for cardiac antibody and 25 controls who were negative for such antibodies (six DCM, six ischaemic or valvular heart failure, 13 normal subjects). Crude myofibrillar proteins, extracted from fresh frozen human atrial or ventricular specimens with alkaline pyrophosphate buffer, were used as antigens. .Sodium dodecyl sulphate polyacrilamide gel electrophoresis (SDS-PAGE) of myofibrillar proteins (5 μl/lane) was performed (Laemmli's method) with 10% and 4% polyacrilamide gels. The proteins were electrophoretically transferred to nitrocellulose sheets (Towbin's method); the paper strips were then incubated in serum samples at 1/100 dilution for two hours. The reaction was revealed with a peroxidase labelled second antibody against human immunoglobulin. On western blotting 12 of the 14 (86%) DCM serum samples containing heart specific antibodies reacted with both the α and β isoforms of myosin heavy chains; none of the 13 normals ($p = 0{\cdot}0001$) and one of the 12 heart failure negative control serum samples (8%, $p = 0{\cdot}0002$) contained antibodies against myosin heavy chains. In contrast, controls and patients had antibodies to ventricular myosin light chain isoform 1 (MLC-1v): DCM serum samples (8/14, 57%), heart failure negative control serum samples (4/12, 33%), and normal samples (2/13, 15%, p = NS).

These findings indicate that α and β cardiac myosin heavy chain isoforms are major autoantigens in patients with dilated cardiomyopathy.

Diversity of myosin heavy chain mutations that cause familial hypertrophic cardiomyopathy

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Familial hypertrophic cardiomyopathy has been defined as a heart muscle disorder of unknown aetiology. Recently we showed that mutations in the α and β cardiac myosin heavy chain genes cause familial hypertrophic cardiomyopathy in some but not all families. Two myosin heavy chain gene mutations have been characterised to date: affected individuals from one family have an α/β hybrid gene while affected individuals from an unrelated family have a β missense mutation. To determine the proportion of familial hypertrophic cardiomyopathy that is attributable to mutations in the myosin heavy chain locus we have begun a systematic screening of the peptide encoding sequences in the α and β cardiac myosin heavy chain genes. Single exons, derived from DNA obtained from affected individuals in 40 unrelated families with familial hypertrophic cardiomyopathy, were amplified by the polymerase chain reaction and examined by a combination of denaturing gradient gel, single stranded conformational polymorphism, and ribonuclease protection analysis. To date, new missense mutations have been identified that alter highly conserved amino acids in four families. The sites of these mutations suggest a clustering effect in a region of the globular head of the myosin heavy chain molecule.

Assessment of the diversity of the mutations causing familial hypertrophic cardiomyopathy will provide new insights into the myosin heavy chain functional domains and may suggest additional candidate proteins for causing the disease in families not linked to chromosome 14q11-12. In addition, identification and localisation of myosin heavy chain mutations will facilitate development of diagnostic probes for familial hypertrophic cardiomyopathy.

Changes in expression of β myosin heavy chain and c-myc genes in left and right ventricles of spontaneously hypertensive rats

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It is proposed that processes that stimulate cardiac hypertrophy are coupled to control of cardiac mass through signal transduction pathways mediated by proto-oncogene products such as c-myc. To examine the role of c-myc in the development of hypertrophy and its association with expression of "fetal" contractile proteins we compared concentrations of β myosin heavy chain (MHC) and c-myc mRNAs in spontaneously hypertensive rats with those in Wistar Kyoto controls at 1–84 days after birth ($n = 8$–10 in each group). β MHC and c-myc mRNAs were measured in left and right ventricles by northern and dot hybridisation to specific oligonucleotides and cDNAs respectively. An increase in heart weight was evident in spontaneously hypertensive rats by three days (52·9 (SE 1 5) mg *v* 33·5 (1·1) mg, $p < 0{\cdot}05$), with similar differences in weight maintained up to 84 days. Transient stimulation of left ventricular c-myc mRNA was seen at one and three days with no difference from controls at later points (day 1, 0·84 (0·07) optical density units/total mRNA *v* 0·5 (0·11) ($p < 0{\cdot}01$); day 3, 4·12 (0·06) *v* 1·11 (0·21) ($p < 0{\cdot}005$)); this preceded an increase in left ventricular β MHC mRNA at 9, 14, and 35 days (day 9, 0·95 (0·14) *v* 0·53 (0·11) ($p < 0{\cdot}05$); day 14, 1·99 (0·29) *v* 1·26 (0·22) ($p < 0{\cdot}05$); day 35, 1·98 (0·31) *v* 1·33 (0·23) ($p < 0{\cdot}05$)). In the right ventricle there were reductions in β MHC and c-myc mRNAs in spontaneously hypertensive rats between 14 and 85 days, changes not seen earlier (β MHC: day 14, 0·36 (0·12) *v* 3·66 (0 82) ($p < 0$ 01); day 35, 0·24 (0 09) *v* 0·98 (0·45) ($p < 0{\cdot}005$); day 84, 0·14 (0·03) *v* 0 30 (0·08) ($p < 0{\cdot}005$). c-myc: day 14, 3·25 (5·83) *v* 5·83 (0·85) ($p < 0{\cdot}05$); day 35, 3·04 (0·9) *v* 8·54 (1·2) ($p < 0{\cdot}005$); day 84, 0·23 (0 07) *v* 0·25 (0·05) ($p < 0{\cdot}005$)).

Transient stimulation of c-myc in the left ventricle is in accord with a role in cardiac growth as well as maintenance of β MHC expression; later hypertrophic growth in spontaneously hypertensive rats in the absence of myc stimulation indicates that myc is not an essential signal for increases in cardiac mass. Reductions in right ventricular β MHC and c-myc mRNAs are compatible with a reduction in right ventricular load in this model of hypertrophy.

Assessment of atrial morphology by paediatric transoesophageal echocardiography

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Atrial morphology was prospectively evaluated in 86 unoperated children with congenital heart disease (age 0·2–14·8 years, mean 3·8 years) by both transoesophageal (TOE) and transthoracic echocardiography (TTE) to determine the diagnostic accuracy of both techniques and to define the potential contribution of TOE in patients with atrial septal defects. The information derived from these studies was correlated with one another and with that obtained by subsequent surgical inspection (53 patients) or by cardiac catheterisation, or both (78 patients). TOE allowed the visualisation of both atrial appendages and thus the direct diagnosis of atrial situs in every case. This was not possible in any patient by TTE. Right and left atrial isomerism was defined in two patients each. In one patient TTE suggested left atrial isomerism, but she was diagnosed as having situs solitus by TOE. Left juxtaposition was defined in four patients by TOE but in only one by TTE. All four had subsequent confirmation. Patency of the oval fossa was shown in 21 patients by TOE and in only 10 by TTE. Left heart catheterisation could be performed through the oval fossa in 17 of these patients. In two children secundum atrial septal defects were identified by TOE that had been missed by previous TTE. In the remaining 26 children with secundum defects TOE allowed a better definition of the relation of the defect to the pulmonary veins, the tricuspid valve, and the coronary sinus. In particular the anterosuperior rim of the defect was consistently better visualised by TOE. Redundant oval fossa flap valves were readily identified by TOE. In three children sinus venosus defects were identified by TOE that had been missed by TTE. All five had subsequent confirmation. Multiple atrial septal defects were documented in four patients by TOE and in only one by TTE. Primum defects were equally well documented by either technique (nine patients). A subtotal cor triatriatum was diagnosed in one child only by TOE and was subsequently confirmed on surgical inspection.

TOE provides an improved evaluation of atrial morphology when compared with transthoracic echocardiography. It provides the direct diagnosis of atrial situs and juxtaposition of the atrial appendages. The atrial septum is documented in much more detail by TOE than by TTE. Thus TOE may be expected to have a major impact on patient selection for transcatheter closure of atrial septal defects.

Monitoring interventional cardiac catheterisation by paediatric transoesophageal echocardiography

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Paediatric single plane transoesophageal echocardiography was used in 17 children scheduled for interventional cardiac catheterisation (six balloon dilatation of the pulmonary valve, four balloon dilatation of the aortic valve, one pulmonary angioplasty, two aortic angioplasty, two duct occlusion, and two Mustard baffle dilatation) to determine its potential value as a dedicated monitoring technique. The age at investigation ranged from 0·9 to 14·6 years (mean 6·0 years), the weight from 9·5 to 49·2 kg (mean 22·8 kg). The transoesophageal studies were completed in all patients without complications being encountered. Procedure time was not prolonged in any case. Preintervention studies provided important new information in two patients, which led to the cancellation of the procedure. The technique allowed real time assessment of catheter placement across the aortic valve and the relation of the catheter to the atrioventricular valves during balloon dilatation of valves and duct occlusion. Chordal rupture of the tricuspid valve was documented in one child. In a further two patients balloon position with respect to the atrioventricular valves was modified according to the transoesophageal findings. Immediate changes in aortic valve morphology and function during balloon dilatation of the aortic valve were able to be closely monitored and aortic regurgitation could be excluded before each balloon inflation. In contrast, only little information on pulmonary valve morphology and function could be obtained. Localised dissection of the descending aorta or the branch pulmonary artery could be excluded during angioplasty procedures. Transcatheter occlusion of a ductus arteriosus was not enhanced by single plane transoesophageal monitoring. Valuable morphological and haemodynamic information on systemic venous pathway obstructions and enhanced guidance of catheter position was provided during Mustard baffle dilatations.

Paediatric transoesophageal echocardiography is a new important guidance and monitoring technique during interventional cardiac catheterisation in children. It provides additional important morphological information, the immediate identification or exclusion of complications, and the assessment of haemodynamic changes.

Hypoplastic left heart syndrome: increasing antenatal detection is associated with diminishing prevalence postnatally

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During the past 10 years over 600 cases of congenital heart disease have been detected prenatally, of which 101 cases were the hypoplastic left heart syndrome. Seventy three of these cases were seen in the past three years, the rise in detection rate being related to the introduction of four chamber view screening on routine obstetric scans. Of the 101 cases, 83 (82%) were referred because the four chamber view was thought to be abnormal. Of 74 cases diagnosed before 24 weeks' gestation, the majority of parents (85%) elected to terminate the pregnancy when counselled about the prognosis. There were three intrauterine deaths so that of a possible 101 infants, only 35 reached postnatal care. None of these 35 infants survived. Although the Norwood procedure or cardiac transplantation are potentially available to treat these infants, the results are still poor. The majority of infants are not treated and die in the neonatal period. Two mothers in our series elected for transplantation but in neither infant was the procedure successful.

Simultaneously with the increase in the numbers detected prenatally has occurred a fall in the number of cases seen in a regional paediatric cardiology centre from 14 to 16 cases in 1986 and 1987 respectively to eight, seven, and six cases in 1988, 1989, and 1990 respectively. If the four chamber screening programme is extended nationwide this condition could almost disappear from postnatal practice.

Hypoplastic left heart syndrome: is transplantation the answer?

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The hypoplastic left heart syndrome (HLHS) is the commonest cause of neonatal death from congenital heart disease. Cardiac transplantation now offers the prospect of a medium term survival of up to 80% but will only become a reality if suitable infant donors are available. We performed a retrospective survey of deaths from HLHS to assess the potential need for neonatal cardiac transplantation and of deaths from anencephaly and head injury to try to identify potential donors. Data for the Northern region, 1982–9 were obtained from the Regional Surveys of Perinatal Death and Fetal Abnormality, the Office of Population Censuses and Surveys, hospital records, and coroners' reports. Forty one cases of HLHS were identified (median six per year; 1:6700 live births). Nine out of 41 (22%) were unsuitable for transplantation because of prematurity (seven) or multiple congenital abnormalities (two), leaving 32 potential recipients. Since November 1986 nine out of 20 cases of HLHS (45%) were diagnosed in utero and in seven the pregnancy was terminated. In 1982–9 there were no liveborn fetuses with anencephaly >2500 g birth weight and >35 weeks' gestation. From 1979–86, 30 infants died of head injury but 29 out of 30 (97%) would have been unsuitable as cardiac donors because of size >8 kg (nine), early death (12), non-accidental injury (seven), or cardiac injury (one).

We conclude that the numbers of infants dying of anencephaly or head injury will not be sufficient for neonatal transplantation. If cardiac transplantation is to be used in HLHS an alternative source of donors will have to be identified. The introduction of widespread fetal echocardiographic screening may drastically reduce the number of liveborn children with HLHS.

Does altitude accelerate the progression of pulmonary vascular disease in children with left to right shunts? A quantitative morphometric lung biopsy study

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The chronic hypoxia of altitude has been shown to raise pulmonary vascular resistance in inhabitants of the high Andes and the Himalayas. The effect of altitude on pulmonary vascular resistance in children with congenital heart defects is unknown. We studied 19 children, aged 4 months to 15 years (median 11 months), with left to right shunts (ventricular septal defect (VSD) eight, ductus arteriosus (DA) seven, both VSD and DA four) from Johannesburg, South Africa (1800 m). All patients had equal systemic and pulmonary artery systolic pressures at cardiac catheterisation. Ratio of pulmonary to systemic flow ranged from 0·44 to 3·1 (mean 1 6) and pulmonary arteriolar resistance index (PARIx) from 4·2 to 25·5 μm^2 (mean 9·7) in air. Pulmonary vascular resistance was reactive as shown by a fall of PARIx $>2\ \mu m^2$ in seven out of 11 patients with administration of oxygen. Lung biopsy specimens taken at the same admission were studied with quantitative morphometric techniques. Results were compared with normal values at sea level and with those in patients with VSD at sea level. All patients showed increased muscularity of arteries with extension of muscle to peripheral intra-acinar arteries. All had "arterialised" veins. Intimal change was present in 10 patients (mild in seven, severe in three). Percentage wall thickness of pre-acinar arteries was 14–39 (normal, sea level 5·8–6·4 ($p < 0{\cdot}001$); VSD, sea level 8·0–13·3 ($p < 0{\cdot}001$)). Mean percentage wall thickness of 51–100 μm arteries was 22·7 (normal, sea level 7·4 ($p < 0{\cdot}001$); VSD, sea level 16·2 ($p < 0{\cdot}001$)) and of $<50\ \mu m$ arteries was 26·4 (normal, sea level 9·6 ($p < 0{\cdot}001$); VSD, sea level 21·9 ($p < 0{\cdot}05$)). Arterial size (external diameter of arteries accompanying respiratory bronchioli) and arterial numbers (alveolar-arterial ratio) were both within normal limits. In cases of VSD at sea level structural changes in the pulmonary arteries were related to age and pulmonary vascular resistance. In our series no such relation was seen.

Children with left to right shunts who live at moderate altitude have increased muscularisation of pulmonary arteries compared with that in their counterparts at sea level. Interestingly, however, they show no reduction in arterial size or numbers unlike those at sea level.

Advanced pulmonary vascular disease: 24 hour urinary excretion of vasoactive eicosanoids

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Prostacyclin (PGI_2) and thromboxane (TXA_2) have opposing actions on pulmonary vascular smooth muscle and platelets and PGI_2 is used in the treatment of pulmonary hypertension. We have, therefore, investigated eicosanoid biosynthesis in 18 patients with advanced pulmonary vascular disease (age 11–24 years, median 17·5 years; mean pulmonary vascular resistance (PVR) 17·5 Um^2) and in 56 controls (age 11–40 years, median 20). We also studied 18 patients (age 0·2–2·25 years, median 0·9 years) with a left to right shunt and a high pulmonary blood flow but reversible pulmonary vascular changes (mean PVR 2·5 Um^2) and seven controls (age 0·9–2·25 years, median 1·3 years). Twenty four hour urinary concentrations of the PGI_2 metabolite 2,3-DN-6-oxo-PGF1a and the TXA_2 metabolite 2,3-DN-TXB_2 were measured by immunoaffinity chromatography and gas chromatography electron capture mass spectrometry. In patients with advanced pulmonary vascular disease the mean urinary concentration of 2,3-DN-6-oxo-PGF1a was 139 (SEM 19) ng/g creatinine, significantly lower than that in the controls (184 (13)) ($p < 0·05$), and the 2,3-DN-TXB_2 was 376 (54), significantly higher compared with the controls (272 (19)) ($p < 0·05$). In the younger patients with high pulmonary blood flow the 2,3-DN-6-oxo-PGF1a concentration was 437 (43) (control 514 (113)) and 2,3-DN-TXB_2 concentration was 1287 (148) (control 858 (213)).

PGI_2 and TXA_2 biosynthesis may be higher in younger children when the pulmonary vascular bed is more labile than later. In advanced pulmonary vascular disease there may be an imbalance in eicosanoid biosynthesis which favours vasoconstriction and platelet aggregation and this trend may exist before the development of irreversible pulmonary vascular changes.

Study of low dosage prostaglandin: usage and complications

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Low dosage intravenous (<0·01 μg/kg/minute) and oral prostaglandin E have been reported to produce fewer complications than higher intravenous doses (0·02–0·1 μg/kg/minute) in the manipulation of the arterial duct for congenital heart disease. Over a three year period 34 neonates (aged 30 weeks' gestation to three weeks; weight 1·45–3·86 kg) were treated with low dosage intravenous or oral prostaglandin for cyanotic (29) and acyanotic (six) lesions. Eighteen (53%) had complications associated with this treatment, with 14 having more than one complication. Major complications occurred in nine (26%) patients—necrotising enterocolitis (seven), apnoea or bradycardia, or both (five), convulsions (one), haemorrhage (one)—and required a change of management. The factors common to all neonates who developed necrotising enterocolitis were cyanotic congenital heart disease, prostaglandin administration, and enteral feeding. All four premature infants in this study developed necrotising enterocolitis. Other complications included feeding intolerance (seven), pyrexia (four), clinical heart failure (three), tachypnoea (two), thrombocytopenia (two), and jitteriness (one).

In contrast to other studies, we report a similar high incidence of complications with low dose intravenous and oral prostaglandin as has been reported in the use of high intravenous dosage. Prostaglandin usage in any form deserves caution.

Comparative aortic root measurement in controls and in children and adolescents with Marfan's syndrome

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Functional aortic root involvement is well recognised in adult patients with Marfan's syndrome, but less is known about aortic root involvement in younger patients. Furthermore, confusion about which regions of the aortic root to measure serially and the absence of suitable normal centiles for comparison make interpretation of such measurements difficult. By retrospectively reassessing the aortic root dimensions from stored images (obtained by cross sectional echocardiography) in 378 children and adolescents with innocent murmurs normal centiles for four separately recognisable regions of the root were obtained. These regions included (*a*) valve annulus, (*b*) sinuses of Valsalva, (*c*) sinotubular junction, and (*d*) proximal ascending aorta. Corresponding retrospective measurements from follow up data in 41 patients with Marfan's syndrome aged up to 21 years were obtained for comparison. In patients with Marfan's syndrome the earliest change observed was in the sinus of Valsalva region, which dilated progressively prepubertally to above the 90th centile for age and body surface area but which was not accompanied by aortic incompetence. It preceded postpubertal dilatation of the annulus, the latter heralding the onset of valve incompetence.

We conclude that in Marfan's syndrome the four regions within the aortic root should be sequentially measured by cross sectional echocardiography, with particular attention being paid to the valve annulus.

Absent pulmonary valve syndrome: surgery in infants with airway obstruction

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From 1979 to 1989, 17 infants with the absent pulmonary valve syndrome and severe airway obstruction underwent extensive pulmonary aneurysmorrhaphy utilising cardiopulmonary bypass (age range 4 days–14 months, mean 5·4 months; weight range 1·7–9·3 kg, mean 4·8 kg). Twelve of these patients underwent associated transatrial ventricular septal defect (VSD) closure and infundibular resection and a short transannular patch. Two underwent transventricular VSD closure and infundibular resection and no transannular patch; one underwent transventricular VSD closure and transannular patch. Two patients underwent pulmonary aneurysmorrhaphy alone. All 17 infants left the operating theatre with good haemodynamic function. Three patients (two premature, weighing 1·7, 2·3 kg) died (hospital mortality 17·6%) postoperatively (12 days–5 months) because of severe airway obstruction that could not be relieved despite further tracheobronchopexy procedures in two of the three patients. One of the 14 patients discharged from hospital died subsequently after reoperation. This patient, the first in the series, was found to have an undetected, obstructed right pulmonary artery from redundant wall at necropsy. Four other patients successfully underwent reoperation—pulmonary artery branch stenosis in two, closure of a previously unrepaired VSD in one, and branch pulmonary artery stenosis with significant pulmonary incompetence (PI) in one. In the remaining nine survivors PI was present but currently well tolerated. In two the right ventricle was dilated but contracting well. In seven right ventricular size was within normal limits. There were 13 long term survivors (range of follow up 3 months–7 years, mean 52·3 months). Eight of the 13 had episodic wheeze of mild to moderate severity that was responsive to sympathomimetic bronchodilator aerosols. The remaining five were free of symptoms.

The insertion of a pulmonary valve at operation may well not be necessary for a successful outcome. It may, however, need to be inserted at a later date because of free PI and right ventricular dilatation, as has occurred in one patient to date.

Pulmonary atresia, ventricular septal defect, and hypoplastic pulmonary arteries with major aortopulmonary collaterals: use of central end to side shunt as staging procedure

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Twenty eight patients with pulmonary atresia, ventricular septal defect, hypoplastic pulmonary arteries with major aortopulmonary collaterals (MAPCAs), and very small pulmonary arteries underwent a direct central end to side shunt as a staging procedure between 1980 and 1989. Age range was 2 months–32 years, with 19 patients under 1 year of age. Two patients had an absent left pulmonary artery and 26 a confluent main pulmonary artery, right pulmonary artery, left pulmonary artery system. Pulmonary artery diameter was 1–1·9 mm in seven patients, 2–2 9 mm in 17, and 3–3·9 mm in four. The central shunt was the initial staging procedure in 27 patients. There were three hospital deaths (10·7%) (70% confidence interval 5% to 20%), including one patient who went through the unifocalisation and correction in the one hospital admission. Major complications in the 25 survivors included congestive cardiac failure from over shunting in 10 (mild to moderate with no haemodynamic instability in eight and severe ventilator dependent in two, both of whom then successfully proceeded through unifocalisation to correction within one month), endocarditis in one, and tamponade associated with pericardial closure in one. There were 25 survivors of the first hospital admission and, of these, 13 proceeded through unifocalisation to correction (ventricular septal defect patch fenestration, one patient) with no deaths, including two patients who underwent shunting, unifocalisation, and correction successfully during the first hospital admission (overall 14 corrections with one death). Seven patients await further surgical staging. In four patients further staging has been suspended because criteria for correction (pRV/LV < 0·7, no remaining sizable hypoplastic pulmonary arteries with major aortopulmonary collaterals, two out of three lung segments connected to native pulmonary arteries) have not been achieved in three patients, and one adult patient, much improved by the central shunt, has currently withdrawn from the programme. There was one late death four months after a fourth preparatory operation (open mitral valvotomy for mitral stenosis). Proximal right pulmonary artery stenoses occurred in 75% of patients (70% confidence interval 63% to 85%) and left pulmonary artery stenoses in 50% (70% confidence interval 38% to 62%), but overall satisfactory pulmonary artery growth was achieved in 75% of hospital survivors (70% confidence interval 63% to 85%) investigated postoperatively (n = 24). A philosophy of early entry into a staged programme has evolved.

Aorta-pulmonary window: an echocardiographic "blind spot"

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Though case reports indicate that cross sectional echocardiography (2DE) can diagnose isolated aortopulmonary window (APW), the accuracy of diagnosis is unknown. We therefore reviewed all 16 patients (age 1 day–2 years, median 3 months) with APW seen since 1982, when routine 2DE became available at our institution. When APW was an isolated lesion (seven patients) initial 2DE diagnosed the lesion in all but one. The exception was a cyanosed, dysmorphic neonate with persistent fetal circulation. The APW was identified on the second 2DE examination when she next presented aged 4 months with heart failure. In nine patients APW was associated with other cardiac abnormalities (ventricular septal defect (VSD) in three, coarctation of the aorta (COA) in three, tetralogy of Fallot in two, right aortic arch (RAA) in one). The APW was diagnosed on the initial 2DE in only three of these. APW was diagnosed at the second 2DE examination in three patients (two after repair of COA and one with RAA in whom the initial study was technically inadequate in an unsedated infant). In the remaining three patients, all with VSD, the APW was detected at angiography. On review of the initial 2DE videotapes in the seven patients in whom APW had been "missed" the lesion could be seen in all six of those with technically adequate studies, suggesting that the APW had been overlooked. The APW was best imaged by subcostal paracoronal and parasternal short axis views. Colour flow Doppler ultrasonography helped to confirm the diagnosis in the three patients seen since this technique became available. No false positive diagnosis of APW occurred.

Though 2DE can reliably diagnose APW when it is an isolated lesion, APW can be overlooked when other cardiac abnormalities are present. In patients with VSD or aortic arch abnormalities APW must be specifically excluded.

What happens to neonates with Ebstein's anomaly?

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Little is written about the natural and postsurgical history of Ebstein's anomaly (EA) in neonates. The only report (on 11 neonates) showed high early mortality but good outcome in those who survived the first three months. We reviewed 48 neonates with EA seen from 1960–89, presenting at a median age of 2 days. Over half of the cases (31/48 (64%)) had been diagnosed since 1980 by echocardiography. Twenty six had cardiac catheterisation at some time, with a high procedure related complication rate (11/26 (42%), including two deaths). Associated defects (other than atrial septal defect) included pulmonary stenosis (in nine) and atresia (in seven). Eighteen patients had surgery (aged 1 day to 18 years; palliative in 12 and intracardiac in six). Nine patients died as neonates (18%)—six of heart failure whose condition was thought to be inoperable, two suddenly, and one perioperatively. In the 39 patients surviving the first month there were 15 late deaths (38%)—five sudden (one of these late after surgery), four perioperatively, three with heart failure, two at cardiac catheterisation, and one non-cardiac. Actuarial survival at 10 years was 50%. Five others whose condition had improved as neonates returned 1–8 years later with arrhythmia or heart failure, but in these children symptoms improved after surgical or medical treatment. Twenty four survivors were in functional class I or II after a mean follow up of 8·8 years.

Early mortality in EA was therefore high. However, even those who survived the neonatal period were at considerable risk of late arrhythmia, haemodynamic deterioration, and death.

Pulmonary blood flow after right heart bypass surgery: role of the lungs

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With pulsed wave, transthoracic and transoesophageal Doppler echocardiography and simultaneous respirometry the effect of changes in intrathoracic pressure on pulmonary blood flow was studied in 12 patients after the Fontan procedure (FP) and in three patients after total cavopulmonary anastomosis (TCPA). In patients after FP a biphasic pattern of pulmonary blood flow was observed, coincident with atrial and ventricular systole. Normal inspiration caused a significant increase in forward flow in the pulmonary artery by a factor of 1·8 compared with expiration ($p = 0{\cdot}004$). In patients after TCPA blood flow into the pulmonary artery was synchronous with inspiration, while the development of a larger negative intrathoracic pressure of −25 cm H_2O during a Mueller manoeuvre markedly augmented pulmonary blood flow. During a brief Valsalva manoeuvre (25 cm H_2O) there was flow reversal in the pulmonary artery. In both groups of patients large increases in pulmonary blood flow occurred when the chest was expanded by using a negative extrathoracic pressure cuirasse, while the development of a positive pressure in the cuirasse caused flow reversal.

After right heart bypass intrathoracic pressure is an important determinant of pulmonary blood flow, which may be increased when negative extrathoracic pressure is used as a means of respiratory support.

Myocardial infarction in childhood: clinical analysis of 17 patients and medium term follow up of survivors

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Myocardial infarction is rare in infancy and childhood. Between 1979 and 1989, 17 patients aged 2 months to 12 years with acute myocardial infarction of any cause (other than after cardiac surgery) were seen. Eight died from three days to three years after diagnosis (overall mortality 47%). The nine survivors, now aged 2–17 years, were followed up for 1 to 10 years (mean follow up 5 years) after infarction. The commonest causes of myocardial infarction were anomalous origin of left coronary artery from the pulmonary artery (six patients (35%)) and Kawasaki disease (five patients (27%)). The main symptoms of acute myocardial infarction were dyspnoea, vomiting, and difficulty in feeding. Diagnosis was made in all cases by electrocardiography and confirmed by echocardiography, by cardiac catheterisation, or at operation. All survivors were free of symptoms and had excellent exercise capacity. Left ventricular ejection fraction in survivors ranged from 21% to 66%, and only one child took regular cardiac drug treatment. There were no cases of late sudden death. Twenty four hour Holter monitor performed on survivors gave normal results (seven cases) or showed only minor abnormalities (one case), suggesting that serious arrhythmia is rare after paediatric myocardial infarction.

Myocardial infarction in children has a high early mortality. However, survivors have a low incidence of serious arrhythmia and have good exercise tolerance even in the presence of a low left ventricular ejection fraction.

Activation of ATP sensitive potassium channels is involved in endothelium dependent relaxation induced by acetylcholine in rabbit coronary arteries

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Hyperpolarisation may contribute partially to endothelium dependent vascular relaxation. This study assessed the possible inhibitory effects of glibenclamide and barium, inhibitors of ATP sensitive potassium (K^+) channels, on endothelium dependent relaxation. Coronary artery rings ($n = 6$ in each group, mean (SEM)) with and without endothelium from adult male New Zealand white rabbits were suspended in individual organ baths containing modified Krebs solution at 37°C and bubbled with 95% oxygen and 5% carbon dioxide. Changes of tension were recorded at a resting tension of 1 g. Rings were equilibrated for 90 minutes before K^+ (30 mM) or prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$, 3 μM) was added. Acetylcholine (0·1 μM) induced relaxation by 47% (4%) of K^+ evoked contraction (0·8 (0·1 g)) and by 82% (7%) of $PGF_{2\alpha}$ evoked contraction (0·7 (0·2 g)) in rings with endothelium. Glibenclamide (3 μM) had no constrictor effect on resting and precontracted endothelium intact rings. Barium (1 mM) induced slight but non-significant contraction in precontracted rings. Glibenclamide and barium partially inhibited the relaxation induced by acetylcholine. Glibenclamide (dissolved in ethanol, 3 μM) reduced relaxation induced by acetylcholine (0·1 μM) in K^+ (30 mM) and $PGF_{2\alpha}$ (3 μM) precontracted endothelium intact rings to 41% (5%) ($p < 0{\cdot}05$) and 71% (6%) ($p < 0{\cdot}05$) respectively. Likewise barium (1 mM) reduced the relaxation induced by acetylcholine (0·1 μM) in K^+ and $PGF_{2\alpha}$ precontracted rings to 39% (5%) ($p < 0{\cdot}02$) and 69% (5%) ($p < 0{\cdot}01$) respectively. Acetylcholine (0·1 μM) induced no significant relaxation in rings without endothelium.

These results suggest that activation of ATP sensitive K^+ channels is part of the mechanism of the endothelium dependent relaxation induced by acetylcholine in isolated rabbit coronary artery preparations.

Cyclic guanosine monophosphate inhibits cardiac α_1 adrenergic induced positive inotropy and phosphatidylinositol hydrolysis

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α_1 Adrenergic induced positive inotropic effects are associated with and may be due to phosphatidylinositol (PI) hydrolysis and generation of the intracellular second messenger inositol trisphosphate (IP_3). In vascular smooth muscle cyclic guanosine monophosphate (cGMP) inhibits noradrenaline induced IP_3 production, but its role in myocardium is not established. We studied the effects of four different cGMP increasing interventions on phenylephrine (PE) induced inotropic effects and IP_3 concentrations (measured by a selective protein binding assay) in isolated ferret papillary muscle preparations (with 1 μM acebutolol and 10 mM lithium chloride). PE (1 nM to 10 μM) had a concentration dependent positive inotropic effect, at 10 μM increasing isometric force by 22% (4%) and unloaded shortening velocity (V_{max}) by 25% (4%) ($n = 14$) and IP_3 content by 59% ($n = 10$). In muscle preparations stimulated by 10 μM PE ($n \geqslant 8$) a threefold to sixfold increase in cGMP concentration by 1 μM 8-bromo cGMP, 1 μM sodium nitroprusside, or 1 μM atrial natriuretic peptide (stimulants of soluble and particulate guanylate cyclase respectively) or 0·1 μM substance P (which releases endothelium derived relaxing factor from endocardium) significantly ($p < 0{\cdot}05$, analysis of variance) reduced the inotropic response (for example, V_{max} decreased by 46%, 59%, 78%, and 86% respectively) and the IP_3 response (by 128%, 161%, 142%, and 140% respectively).

These results show that cGMP elevation inhibits both inotropic and IP_3 responses to cardiac α_1 adrenergic stimulation and are consistent with a role for PI hydrolysis in mediating α_1 positive inotropic effects.

Platelet mediated alterations in cardiac cellular electrophysiology during normal perfusion and myocardial ischaemia

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Recent clinical and experimental evidence indicates that platelet activation contributes to the arrhythmogenic effects of myocardial ischaemia. To investigate the mechanisms responsible we studied the changes in cellular electrophysiology and arrhythmogenesis during infusion of platelets (10^8/ml) in isolated, perfused guinea pig hearts during normal perfusion and global myocardial ischaemia. Hearts were studied in four groups: A ($n = 9$) buffer only; B ($n = 9$) buffer and platelets pretreated with 1 μM forskolin; C ($n = 8$) buffer and platelets pretreated with 10 μM forskolin; D ($n = 3$) as in group B but with frozen and thawed (activated) platelets. Infusion of platelets (groups B and C) had no effects during normal perfusion, but activated platelets (group D) decreased action potential duration (APD) from 164 (1) ms to 134 (4) ms at 15 minutes of normal perfusion ($p < 0{\cdot}05$) and produced ventricular fibrillation in all three at 21 (1) minutes. During ischaemia platelets (group B) increased the incidence of ventricular fibrillation (100% v 56% group A, $p < 0{\cdot}05$) but this was prevented by 10 μM forskolin (group C 50% v 100% group B, $p < 0{\cdot}02$). Platelets in group B enhanced the ischaemia induced reductions in APD (126 (2) ms v 139 (3) ms (group A), $p < 0{\cdot}01$ at 5 minutes), but these were attenuated with platelets pretreated with 10 μM forskolin (group C 147 (5) ms v 126 (2) ms group B, $p < 0{\cdot}01$ at 5 minutes). Hearts in group C took longer to develop arrhythmias during ischaemia than those in group B (21 (2) min v 15 (1) min, $p < 0{\cdot}02$) and recovered more rapidly during reperfusion.

These studies show (*a*) that infusion of activated platelets produces deleterious electrophysiological and arrhythmogenic effects in normally perfused hearts and (*b*) that myocardial ischaemia causes platelet activation, which contributes to the electrophysiological and arrhythmogenic effects observed.

Fractionation of paced right ventricular electrograms in hypertrophic cardiomyopathy

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Patients with hypertrophic cardiomyopathy who have developed clinical ventricular tachycardia (VT) or fibrillation (VF) or who have died suddenly have no specific electrophysiological abnormality. We have developed a test to quantify the likely electrophysiological features of disarray that may predict which patients with hypertrophic cardiomyopathy are at risk of VT or VF. Variation in fibre calibre may cause changes in local conduction velocities and refractory periods. Disarray may lead to multiple conduction paths between two ventricular sites that may be blocked or recruited with different refractoriness of the intervening tissues. To reveal this effect the right ventricle is paced with two sequences at one site and high pass filtered electrograms are recorded from three other sites. The first sequence of 800 stimuli is a regular drive cycle with an interpolated extrastimulus every third beat with a coupling interval that decreases by 1 ms on each occasion, which generates a set of electrograms that correspond to particular interstimulus intervals. The second sequence of 1600 stimuli has a random interstimulus interval to alter the refractory state of tissue between the pacing and recording electrodes. With one path between the electrodes no change in the electrogram configuration in regular and random pacing would be expected. With multiple paths the electrograms would be expected to fragment as the activation of myocardium within the electrode receptive field changes. Each electrogram is correlated with a set of templates and the number of templates required to fit all the complexes is determined. The variability of a record corresponds to the number of templates that are generated from it. The ratio of the number of the randomly paced templates to the number of regularly paced templates (Trand/Treg) measures the recruitment of paths between electrodes. Of 12 patients with hypertrophic cardiomyopathy, three had no recorded arrhythmias or family history of sudden death, five had such a history, and four had recorded VT or VF. Trand/Treg values were 1·6–3·6, 2·0–6·5, and 2·7–5·8 respectively. The difference between the no arrhythmia, no family history of sudden death, and the pooled family history of sudden death and VT or VF groups was significant by a sign test at $p < 0{\cdot}01$.

These results suggest that this new method of electrophysiological quantification of disarray may help predict the risk of VT and VF in hypertrophic cardiomyopathy.

Assessment of ventricular volumes by single breath nitrogen washout test

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As yet there is no simple, accurate, non-invasive technique for measuring cardiac volumes that would be suitable for routine screening of patients. We describe a new method whereby cardiogenic oscillations observed during the course of a single breath nitrogen washout test are analysed to provide an estimate of cardiac displacement volume. This test is a simple procedure for both patient and operator and can be performed rapidly without resort to sophisticated equipment. Pulsatile changes in partial pressure of nitrogen are transformed to effect a ventricular volume-time curve and yield estimates of the systolic ejection fraction (SEF), mean velocity of circumferential fibre shortening (MVCFS), end diastolic volume (EDV), end systolic volume (ESV), and other indices. A comparison with echocardiographic measurements of left ventricular dimensions in the same group of 20 normal subjects and 12 patients with ventricular disease showed significant linear correlations for SEF ($r = 0\cdot76$, $p < 0\cdot001$) and MVCFS ($r = 0\cdot61$, $p < 0\cdot001$). Echocardiographic values of left ventricular volumes likewise indicated significant correlations in respect of EDV ($r = 0\cdot54$, $p < 0\cdot01$) and ESV ($r = 0\cdot72$, $p < 0\cdot001$).

Thus, the single breath nitrogen washout test gives an accurate assessment of ventricular volume and could be a useful tool for repeated measurements to map patients' progress in units where sophisticated equipment is not available.

Does hyperinsulinaemia cause microvascular angina?

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Coronary microvascular dysfunction may underlie syndrome X—angina and supportive evidence of myocardial ischaemia but normal coronary arteriograms. Hyperinsulinaemia is implicated in the microvascular abnormalities of diabetes and hypertension. We therefore compared oral glucose (75 g) tolerance tests in 11 patients with previously characterised syndrome X (none with overt diabetes or hypertension) and 11 age, sex, and body weight matched controls. Fasting glucose concentration was normal in all subjects, but glucose tolerance was impaired (2 hour glucose concentration $> 7\cdot8$ mmol/l) in six patients with syndrome X compared with two controls ($p < 0\cdot05$). Fasting insulin concentrations were similar, but peak and 2 hour insulin concentrations and the area under the insulin-curve were higher in patients with syndrome X (median 116 (range 60–226) *v* 84 (34–110) $\text{mU/l} \times 10^3$, 100 (35–187) *v* 50 (15–110) $\text{mU/l} \times 10^3$, and 10·4 (5·9–19·2) *v* 6·7 (2·3–11·3) $\text{min} \times \text{mU/l} \times 10^3$ respectively; all $p < 0\cdot01$). Total and low density lipoprotein cholesterol concentrations and total triglyceride concentration were similar in the two groups, but high density lipoprotein cholesterol concentration was lower in patients with syndrome X (mean 0·93 (SD 0·19) *v* 1·32 (0·30) mmol/l; $p < 0\cdot01$).

These findings suggest that hyperinsulinaemia occurs in patients with syndrome X and may thus contribute to the pathogenesis of microvascular angina.

Aging, autonomic function, and perception of angina

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Coronary artery disease is common in the elderly but little is known about the effects of aging on the perception of angina. We studied 90 non-diabetic men aged 35–82 years, all of whom had typical angina, to determine whether age related changes in blood pressure and autonomic function are associated with changes in anginal perceptual threshold—the time from onset of 0·1 mV ST depression to angina during treadmill exercise. The effects of aging on somatic pain threshold (measured by calf sphygmomanometry) were also assessed in a subgroup of 35 patients. Age showed the predicted correlations with blood pressure ($r = 0\cdot3$, $p < 0\cdot001$) and autonomic function as reflected by heart rate responses to Valsalva manoeuvres ($r = -0\cdot4$, $p < 0\cdot001$). Age also showed highly significant correlations with anginal perceptual threshold ($r = 0\cdot3$, $p < 0\cdot005$) and somatic pain threshold ($r = 0\cdot4$, $p < 0\cdot02$), older patients having longer latency between ST depression and angina and tolerating higher cuff inflation pressures. Subgroup analysis confirmed that patients over 65 had higher thresholds for angina (67 (80) *v* 14 (76) s, $p < 0\cdot005$) and somatic pain (228 (66) *v* 156 (74) mm Hg, $p < 0\cdot02$) than the younger group. Neither variable, however, correlated significantly with blood pressure or autonomic function.

In conclusion, this study has shown that the perception of angina diminishes with advancing age. Although the mechanism is unclear, it seems to reflect a generalised hyposensitivity to pain in the elderly and is not solely attributable to age related changes in blood pressure and autonomic function.

Monophasic action potential and detection of myocardial ischaemia in humans: an appraisal using endocardial recordings

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The monophasic action potential (MAP) recorded from the surface of the myocardium provides a sensitive measure of localised myocardial ischaemia. The duration of the MAP shortens in response to ischaemia and commonly registers changes before they appear in an ECG. Although the MAP has been used to document ischaemia on the epicardial surface in both animal and human studies, it has yet to be fully appraised in this context in human endocardial recordings. In a study designed to do so, we compared changes in steady state MAP duration in endocardial recordings between normal and ischaemic areas in patients undergoing routine coronary angiography. Single site

MAPs were obtained from the left or right ventricular endocardium, or both, in 26 patients (32 recording sites) during atrial pacing to angina threshold. Each pacing rate was maintained for two minutes to allow for steady state adaptation. At peak paced heart rate technetium-99m was administered intravenously for subsequent myocardial perfusion scintigraphic imaging and documentation of ischaemia. Eighteen MAP recordings were from areas of myocardium with a normal perfusion pattern and 14 from areas with abnormal perfusion characteristics. MAP duration at 90% repolarisation for every 100 ms change in cycle length shortened by a mean (SD) of 22·1 (4·8) ms in the non-ischaemic regions. The extent of shortening was significantly greater for ischaemic areas, being 33·8 (9·7) ms ($p < 0{\cdot}01$) and indicating the additional effect of ischaemia. As both shortened cycle length and ischaemia abbreviate the MAP duration, a range of values of MAP shortening in unit time was analysed for sensitivity and specificity for detection of ischaemia. A value in excess of 26·5 ms per 100 ms change in cycle length provided the optimum compromise with 88% sensitivity and specificity.

Our results provide validation for the use of endocardial MAP recordings for the detection of ischaemia. The technique would be suited to the evaluation of interventions designed to alter ischaemic responses during catheter directed therapeutic procedures such as coronary angioplasty.

Prognosis after recovery from myocardial infarction: relative importance of cardiac dilatation and coronary stenoses

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We showed previously that long term survival after infarction was best predicted by left ventricular end systolic volume measured after recovery. Surprisingly, the severity of coronary stenoses did not contribute independently to survival, and the present study was done to discover whether a longer follow up would give further information. Male survivors (n = 616, age 50 (7) years) of a first (n = 455) or recurrent (n = 161) infarction had angiocardiography at 4–8 weeks after index infarction and were followed for 8·8 (2·9) years. Coronary surgery was performed in 34%, as a clinical trial in 14%. Angiocardiographic and clinical factors were analysed by the proportional hazards model, taking cardiac death as the end point and considering (*a*) the whole period of observation, (*b*) the first five years after index infarction, and (*c*) the subsequent survival of the survivors at five years. There were 179 deaths, of which 79% were from cardiac causes; of the 141 cardiac deaths, 67% were sudden. End systolic volume remained the most powerful predictor of cardiac death over all time periods. Coronary stenoses (assessed by a scoring system) which were not predictive over 0–5 years became highly predictive after five years. Other independent adverse factors were continued cigarette smoking (19% smoked) and the withholding of β blocking drugs (taken by 34%). Trial surgery, age, and first or recurrent infarction were not predictive.

We conclude that coronary stenoses independently predict cardiac mortality but after a longer time course than ventricular dilatation.

Doppler assessment of effects on cardiac function of oral vasodilators started in early phase of acute myocardial infarction: randomised trial

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Serial changes in stroke volume and cardiac output were assessed by Doppler echocardiography of blood flow in the ascending aorta in patients entered in a randomised double blind trial of an oral angiotensin converting enzyme inhibitor or of an oral nitrate in suspected acute myocardial infarction. Eighty one patients randomised at a mean of 13 hours from the onset of pain to receive 28 days' treatment of captopril (CAP) (12 5 mg three times a day after a 6·25 mg test dose; n = 27), isosorbide mononitrate (ISMN) (20 mg three times a day; n = 22), or placebo (n = 32) were studied. The baseline clinical characteristics and stroke distance of the three groups were similar. Changes in haemodynamic variables were assessed one hour after the first dose, at the time of discharge, and at six weeks—that is, two weeks after the end of trial treatment. At one hour the percentage changes (mean (SEM)) in systolic blood pressure was −11% (2) for CAP, −10% (2) for ISMN, and −1% (1) for placebo ($p < 0{\cdot}001$ for CAP and for ISMN *v* placebo). At discharge and at six weeks there were no differences in systolic blood pressure between the three groups. The percentage changes in stroke volume were: (*a*) at one hour +8% (2) for CAP, 4% (2) for ISMN, and +2% (1) for placebo ($p < 0{\cdot}05$ for CAP *v* placebo); (*b*) at discharge +18% (4), +10% (3), and +7% (3) respectively ($p < 0{\cdot}05$ for CAP *v* placebo); and (*c*) at six weeks +22% (4), +16% (7), and +11% (3) respectively (NS for all comparisons). The percentage changes in cardiac output were: (*a*) at one hour +13% (3) for CAP, +2% (2) for ISMN and +2% (2) for placebo ($p < 0{\cdot}01$ for CAP *v* ISMN and *v* placebo); (*b*) at discharge +23% (5), −1% (4), and −4% (4) respectively ($p < 0{\cdot}001$ for CAP *v* ISMN and *v* placebo); and (*c*) at six weeks +24% (7), 0% (6), and +7% (5) respectively ($p < 0{\cdot}05$ for CAP *v* ISMN and *v* placebo).

In summary, these data suggest that both CAP and ISMN produce a moderate reduction in blood pressure soon after treatment in acute myocardial infarction but that these effects do not persist. Captopril shows a marked increase in cardiac output soon after starting treatment and this effect persists after discontinuation of treatment. ISMN produces less striking haemodynamic improvement but at least shows no sign of reduction in cardiac output when compared with placebo. It seems that both vasodilators can be started safely in the early phase of acute myocardial infarction.

Early and late changes in diastolic filling pattern after myocardial infarction: importance of infarct size

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To characterise the early and late changes in left ventricular filling dynamics associated with myocardial infarction we recorded the Doppler echocardiographic filling patterns in 45 patients (mean age 65 (SEM 1·5) years) at one and six weeks after the acute event. Based on clinical criteria, patients were divided into those with large (group L; n = 12) and those with small infarctions (group S; n = 33). The difference in infarct size was reflected by the peak enzyme activity (AST) in the two groups (553 (59) *v* 212 (22), p < 0·001). These patients were then compared with 16 age matched normal controls (group C). The following filling variables were calculated from the mitral flow velocity waveform: peak early (PE) and peak atrial (PA) velocities (cm/s), early (Ei) and atrial (Ai) velocity integrals (cm). The PE/PA and Ei/Ai ratios were calculated to express the balance between early and atrial filling. To correct for the variation in heart rate, these ratios were divided by the diastolic filling period of the cardiac cycle (PE/PA$_c$, Ei/Ai$_c$). One week after myocardial infarction the PE velocities were higher in group L compared with groups S and C (75 (3), 67 (2), and 62 (4) cm/s respectively; p < 0·01 group L *v* group C, p < 0·05 group L *v* group S). However, there was no significant difference in Ei (9·2 (1), 9·5 (1), and 8·9 (1) cm). Thus, in group L early filling occurred during a shorter early filling period. Although the PA velocities and Ai in group L were not different from those in group S, they were significantly lower compared with those in group C (PA: 59 (5), 69 (2), and 76 (4) cm/s; p < 0·05 group L *v* group C. Ai: 4·0 (0·7), 5·3 (0·2), and 6·4 (0·4) cm; p < 0·01 group L *v* group C). Consequently, the PE/PA, PE/PA$_c$, Ei/Ai, and Ei/Ai$_c$ ratios were higher in group L compared with groups S and C. At six weeks these ratios decreased in group L (PE/PA$_c$ by 25%, p < 0·01; Ei/Ai$_c$ by 22%, p < 0·05) so that the differences between the groups were smaller.

These data suggest that, depending on the size of the infarct, patients with myocardial infarction exhibit a "restrictive" left ventricular filling pattern early after the acute event. This was manifested by the greater proportion of filling occurring in early diastole, reflecting an overall increase in chamber stiffness. Six weeks later the "restrictive" pattern is less pronounced, presumably due to the remodelling process after myocardial infarction.

Combination treatment does not offer an advantage in managing chronic stable angina

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The combination of β blockers and calcium antagonists is widely used in the management of angina pectoris, though there is little evidence to support its efficacy. This double blind randomised crossover placebo controlled study compared the effects of nicardipine, atenolol, and their combination in 30 patients with chronic stable angina and normal (52 (9·6)) left ventricular ejection fraction. Each treatment period lasted six weeks with dose titration after three weeks. Symptom limited treadmill exercise testing and radionuclide ventriculography at rest were carried out at the end of each treatment period. Total exercise duration was significantly prolonged by nicardipine and atenolol (616 s and 592 s respectively) when compared with placebo (529 s). Time to 1 mm ST segment depression was significantly prolonged from 406 s (placebo) to 472 s (nicardipine) and 466 s (atenolol). The combination of nicardipine and atenolol conferred no additional benefit (total exercise duration 610 s and time to 1 mm ST segment depression 483 s). Radionuclide ventriculography showed no significant change in left ventricular ejection fraction with any treatment. The peak filling rate and time to peak filling rate showed no significant change, but there was a significant increase in the first third filling fraction with atenolol (0·59) and the combination (0·6) compared with placebo (0·4). There was also a significant increase in left ventricular end diastolic volume with atenolol (129 ml) compared with placebo (110 ml).

Thus nicardipine and atenolol are effective in prolonging exercise duration in patients with chronic stable angina while the combination offers no additional benefit. Neither drug seems to have an important effect on the parameters of diastolic function studied.

Extent of coronary atherosclerosis is different in unheralded acute myocardial infarction compared with uncomplicated chronic stable angina

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It is unclear whether coronary angiographic findings and risk factor profiles differ at initial presentation of acute versus chronic ischaemic heart disease. We studied 102 consecutive patients (males age ⩽60, females age ⩽65) who either had acute myocardial infarction as first ever manifestation of ischaemic heart disease with a concomitant coronary angiogram (55 patients; mean age 50·2 years) or had had stable angina for at least two years with a positive exercise test, no history of any acute event, no Q waves on electrocardiography or akinesis on ventriculography, and angiography performed ⩾2 years from initial symptoms (47 patients; mean age at symptom onset 51·7 years). Risk factors were analysed and observers, blinded to all clinical data, evaluated these angiograms for (*a*) severity (number of vessel diseased, stenoses ⩾50%, occlusions); (*b*) extent (with an index derived by assigning a score of 0–3 per segment depending on the proportion of lumen length irregularity and dividing the sum by the number of visualised segments); (*c*) pattern (discrete = ⩽3 loci of disease never involving more than 50% of the length of any segment or diffuse = anything exceeding this). Patients with unheralded myocardial infarction had less vessel disease than those with uncomplicated stable angina (mean 1·3 (SD 0·8) *v* 2·1 (0·8), p < 0·001), fewer stenoses (2·1 (1·8) *v* 3·9 (1·8), p < 0·001), fewer occlusions (0·6 (0·6) *v* 1·0 (0·9), p = 0·01), and a lower extent index (0·6 (0·5) *v* 1·2 (0·5), p < 0·001). A discrete pattern was present in 54·6% of those with unheralded infarction and in only 8·5% of those with uncomplicated angina (p < 0·001). Age at symptom onset, sex distribution, serum cholesterol concentration, present and past smoking habit combined, and positive family history were similar in the two groups. Hypertension was found twice as frequently in angina (64·4% *v* 30·9%, p < 0·01), and a recent smoking history twice as often in infarction (60% *v* 31·1%, p < 0·01). There were seven diabetic patients in the angina group, and one in the infarction group.

Thus uncomplicated chronic stable angina is associated with appreciably more severe and extensive atherosclerosis and rarely a discrete pattern and a dissimilar risk factor profile compared with unheralded acute myocardial infarction. Such important differences suggest that acute and chronic manifestations of ischaemic heart disease are unlikely to be random expressions of a single underlying pathological process.

Recurrent ischaemic events after thrombolytic treatment: predictive value of symptoms, stress testing, and coronary arteriography

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Recurrent ischaemic events are common after thrombolytic treatment, and identification of patients at risk is important, although no diagnostic test has yet been validated for this purpose. We studied 101 patients treated by thrombolysis who underwent predischarge stress testing and early coronary arteriography. During 10 (7) months of follow up 21 recurrent ischaemic events were documented: unstable angina (15), acute infarction (five), and cardiac death (one). Events occurred most commonly in patients with patency or high grade collateralisation of the infarct related artery ($p < 0\cdot02$). However, none of the electrocardiographic variables measured during stress testing predicted events, although patients with patent arteries exercised longer (516 (186) *v* 434 (198) s, $p < 0\cdot05$). We therefore examined the angiographic data and performed a morphological analysis of the infarct related coronary lesion. Patients with angina tended to have a tighter residual stenosis than those who remained free of symptoms (86% (15) *v* 78% (17), $p < 0\cdot05$), but neither symptoms nor the severity of the stenosis predicted which patients were at risk of recurrent events. Indeed, none of 10 morphological features analysed was of any predictive value apart from arterial ectasia distal to the lesion ($p < 0\cdot01$).

In conclusion, after thrombolytic treatment neither treadmill stress testing nor continuing exertional angina are of value for predicting which patients are at risk of recurrent ischaemic events after discharge from hospital. Angiography is more helpful because patients with residual perfusion of the infarct territory are at greater risk. Nevertheless, lesion morphology and the severity of the residual stenosis provide little additional guidance and should not affect decisions for revascularisation.

Cardiac structure and function in growth hormone deficiency

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It has recently been shown that cardiovascular mortality is increased in patients with hypopituitarism who have replacement therapy with thyroxine and adrenal steroids but not growth hormone (GH). We investigated the effects of GH deficiency on cardiac structure and function in 21 patients (nine men, 12 women; mean age 44 years, range 24–64) with hypopituitarism (mean duration 11 years, range 1–28) and no clinical evidence of cardiovascular disease, diabetes, or hypertension. Cardiac structure and function were assessed with cross sectional echocardiography and Doppler ultrasonography, and treadmill exercise tolerance was assessed with the Bruce protocol. The degree of GH deficiency, assessed by serum concentrations of insulin like growth factor 1 (IGF-1), was 82 4 (45) μg/l. Lean body mass calculated from total body potassium content was 48 (8) kg. All patients had a normal left ventricular mass index (90 (19) g/m^2) and a normal left ventricular ejection fraction (66% (7)). There was, however, a significant correlation between left ventricular mass and serum IGF-1 concentration ($r = 0\cdot51$, $p < 0\cdot03$). Left ventricular mass and left ventricular diastolic function were related to lean body mass ($r = 0\cdot76$ and $0\cdot64$, $p < 0\cdot003$). Six patients had abnormal left ventricular diastolic function (E/A ratio 1·04 (0·2)). The mean exercise duration with the Bruce protocol was 9 0 (3·8) minutes and no patient had chest pain. A significant correlation was observed between the rate-pressure product (maximum heart rate × systolic blood pressure on exercise) and serum IGF-1 concentration ($r = 0\cdot61$, $p < 0\cdot003$). Six patients developed planar ST segment depression > 0·1 mV during exercise testing (maximum ST segment depression 0·17 (0·03) mV). In five of these patients there was rapid resolution of ST segment depression immediately after exercise. One patient developed ST segment depression at four minutes with slow resolution; subsequent coronary angiography gave normal results. Exercise induced ST segment depression was not related to severity or duration of GH deficiency.

These results suggest that left ventricular mass and the maximum cardiac work achieved on exercise are inversely related to the degree of GH deficiency. Patients with hypopituitarism may often have ischaemic like ST segment changes during exercise testing. Follow up studies of these patients during GH replacement therapy are in progress.

Prediction of outcome in severe chronic heart failure

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The need to identify patients at higher risk and predict prognosis in severe heart failure has become increasingly important with the advent of cardiac transplantation. We undertook a retrospective study of 127 patients with chronic heart failure due to coronary artery disease or dilated cardiomyopathy referred to our exercise laboratory for assessment of functional capacity to identify variables predictive of outcome (death or transplantation). The mean follow up time was 14·6 months. The effect of the following variables on outcome were studied both by univariate and multivariate analysis: age, aetiology of heart failure, cardiothoracic ratio on chest radiography, left ventricular end systolic diameter on echocardiography, left ventricular ejection fraction (LVEF) on radionuclide ventriculography, mean dose of diuretic, plasma sodium and urea concentrations, and the peak oxygen consumption on exercise (Vo_2). The group as a whole had severe heart failure with a median LVEF of 17% and a median Vo_2 of 13·7 ml/kg/min. During the period of follow up 23 patients (18%) died and 18 (14%) underwent cardiac transplantation. Although all the variables studied apart from the aetiology of heart failure affected outcome on univariate analysis, multivariate analysis identified three variables that were independent predictors of outcome. In order of importance these were plasma sodium concentration, LVEF, and Vo_2. The predictive power of these variables for outcome was assessed by multivariate linear discriminant analysis. Seventy four per cent of the deaths or transplantations over the entire follow up period or one year could be predicted from the LVEF, plasma sodium concentration, and Vo_2. When patients undergoing transplantation were excluded, 67% of the deaths could be predicted by the above variables.

In patients with severe heart failure the three variables identified are independent predictors of outcome and are useful in assessing the need for transplantation.

Characterisation of left ventricular filling abnormalities in hypertensive subjects

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Left ventricular filling and effect of left ventricular hypertrophy were studied in 70 untreated hypertensive patients and 40 normal controls who underwent cross sectional echocardiography and pulsed mitral Doppler studies. Peak early (E) and late (A) filling velocities, duration of early (TE) and late (TA) filling and total diastole (TD) were measured. Velocity-time integral of early (EI) and late (AI) filling, deceleration slope of early filling (Edec), E/A ratio, ratio of duration early and total diastole (TETD) and of late and total diastole (TATD) were calculated. Patients were classified into three groups: normal controls (group 1), hypertensive patients without left ventricular hypertrophy (n = 25) (group 2), hypertensive patients with left ventricular hypertrophy (n = 45) (group 3) by using echocardiographic left ventricular mass index. Left ventricular mass index (g/m^2) in group 1 was 103·26 (5·8), 105·2 (4·29) in group 2, and 197·63 (74·66) in group 3 (group 1 *v* group 3, p < 0·001).

	Group 1	Group 2	Value (1 *v* 2)	Group 3	Value (2 *v* 3)
E/A	1·45 (0·4)	1 10 (0 3)	<0·001	0·98 (0·3)	<0·05
Edec	490 (112)	375 (83)	<0 006	325 (159)	<0·01
TATD	0 32 (0 07)	0 41 (0·01)	<0·001	0 35 (0 07)	<0·01
A	50 28 (13 3)	70 25 (13 1)	<0·001	73 04 (20 1)	NS
EI	15 4 (3 5)	13·9 (3 1)	<0 02	15 0 (5·6)	NS
AI	7 2 (1 6)	9·96 (2 3)	<0·01	10 2 (4·3)	NS
TETD	0 46 (0 07)	0 52 (0·06)	<0 001	0·55 (0·08)	NS

Impaired left ventricular filling develops in hypertension and may precede the development of echocardiographic left ventricular hypertrophy. Edec and E/A ratio may be a sensitive index of impaired left ventricular filling in such patients.

Long term effects on left ventricular function of treatment for childhood malignancy

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Anthracyclines and thoracic irradiation used in the treatment of childhood malignancy are known to cause early alterations in left ventricular function. The late effects are poorly documented. Ventricular systolic and diastolic function were assessed blindly with M mode and Doppler echocardiography in 44 symptom free patients (mean age 14·7 years, range 8·6–23) and age and sex matched controls between 2 and 17 years (mean 6·2 years) after chemotherapy for childhood malignancy. The patients received anthracyclines and thoracic irradiation (n = 10), anthracyclines alone (n = 20), or neither form of treatment (n = 14). Fractional shortening (FS) was significantly lower in the patients than in controls (control FS: mean 38·24% (SD 3·46), patient FS: 35·83% (5·47); p = 0·015). There was no significant difference in mitral half time or time from mitral valve opening to aortic valve closure (p = 0·142 and p = 0·53 respectively). There was a trend towards the reduction in FS being associated with thoracic irradiation (p = 0·103) rather than anthracycline (mean doxorubicin dose 256 (146) mg/m^2 and mean daunorubicin dose 248 (105) mg/m^2 treatment (p = 0·191).

This study suggests that treatment for childhood malignancy leads to long term reduction in left ventricular systolic function and that this reduction is more closely associated with thoracic irradiation than anthracycline administration.

Thallium-201 perfusion defects in hypertrophic cardiomyopathy

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The use of thallium-201 perfusion scanning in hypertrophic cardiomyopathy is uncertain. Myocardial ischaemia may be an important determinant of symptoms and prognosis. To determine the prevalence and clinical significance of thallium-201 myocardial perfusion defects in hypertrophic cardiomyopathy single photon emission computed tomography, analysed with bullseye polar coordinate maps, was performed in 80 patients aged 14 to 74 years (mean 42). Maximal treadmill exercise testing and cross sectional echocardiography were performed to determine presence of ST segment change and extent and distribution of left ventricular hypertrophy. Fifty three patients (66%) had regional perfusion defects; they were fixed in 28 (35%) patients, reversible in 32 (40%), and a combination of both in seven (9%). Reverse redistribution, a perfusion defect that develops or increases on the delayed image, was present in 28 (35%) patients. Reversible and fixed defects were localised to segments of the hypertrophied myocardium (23/32, 15/28), whereas reverse redistribution was more common in myocardial segments without hypertrophy (18/28; p < 0·01). There was no association of reversible or fixed defects to chest pain or ST depression (≥2 mm) during exercise. Fixed defects were more common in patients with non-sustained ventricular tachycardia (10/15 *v* 18/65; p < 0·005), in those with marked functional limitation (6/12 *v* 22/68; p < 0·05), and in those with a history of syncope (13/27 *v* 15/53; p = 0·08). These three factors together with a family history of hypertrophic cardiomyopathy and sudden death, young age at diagnosis, and progressive left ventricular dilatation with wall thinning were considered to be risk factors for a poor prognosis. Eight out of nine (89%) patients with large fixed defects and seven out of 19 (37%) with small fixed defects had two or more risk factors, whereas only 12 out of 52 (23%) without fixed defects had two or more risk factors (p < 0·001).

These findings indicate that thallium-201 myocardial perfusion defects are common in hypertrophic cardiomyopathy and are associated with features of adverse prognosis but are not related to clinical markers of ischaemia. Prospective evaluation of their prognostic significance is warranted.

Senning operation for complete transposition: experience at Guy's

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Seventy consecutive infants with complete transposition of the great arteries underwent an atrial switch repair by Senning's technique between 1980 and 1990. Associated defects included ventricular septal defects in 20, left ventricular outflow tract obstruction in 10, coarctation of the aorta in two, and the Wolff-Parkinson-White syndrome in one. The age at operation was 7·4 (3) months (range 17 days–17 months) and weight was 6·7 (1·4) kg (3·8–9·8). There were two deaths in hospital (2·8%). During an average follow up of four years (45 days–9·6 years) none of these patients died and currently all but one has unimpaired exercise tolerance. Two patients had superior vena caval obstruction, which was successfully treated by balloon dilatation. Eight patients have arrhythmias—nodal rhythm in four, the sick sinus syndrome in three, and atrial flutter in one—but only three of these patients require antiarrhythmic treatment.

In our experience Senning's operation for complete transposition carries a low operative mortality and serious baffle complications requiring reoperation are rare. The functional state of the surviving patients during medium term follow up has been encouraging, with a low incidence of arrhythmias or right ventricular dysfunction.

Adenosine: selective pulmonary vasodilatation in patients undergoing assessment for cardiac transplantation

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Intravenous adenosine has been shown to decrease selectively pulmonary vascular resistance (PVR) in normal human subjects and in patients with primary pulmonary hypertension. This effect is of potential therapeutic value in the perioperative period in patients with elevated PVR undergoing orthotopic heart transplantation (OHT). In animal studies adenosine has been shown to be a renal vasoconstrictor. The effect of adenosine infusion on human renal blood flow has not been reported. Clearly, renal vasoconstriction might limit the therapeutic use of adenosine in patients undergoing OHT. This study assessed whether adenosine acted as a selective pulmonary vasodilator in seven patients undergoing assessment for OHT. A pulmonary artery thermodilution catheter was inserted and simultaneous measurements were made of systemic and pulmonary haemodynamic function and of renal blood flow by a continuous renal vein thermodilution technique previously validated in vitro and in animal and human studies. Adenosine (0·05 mg/kg/minute) caused selective pulmonary vasodilatation measured by PVR to systemic vascular resistance ratio (15·0 (9) at baseline *v* 11·6 (6) with adenosine ($p < 0{\cdot}03$)). There were no significant changes in other parameters measured. Respective values at baseline and with adenosine were: mean arterial blood pressure 86 (17) *v* 88 (19) mm Hg, CI 2·02 (0·6) *v* 2·13 (0·7) l/min/m^2, PVR 279 (166) *v* 216 (124) dyn.s.cm^{-5}, heart rate 86 (25) *v* 85 (20) beats/minute, renal blood flow 197 (73) *v* 186 (63) ml/minute, and renal oxygen consumption 5·1 (2·5) *v* 4·6 (2·2) ml/minute. No patients experienced any adverse symptoms or atrioventricular block during adenosine infusion.

Previous reports have suggested that adenosine 0·03–0·05 mg/kg/minute is probably the optimal infusion rate for achieving selective pulmonary vasodilatation in humans. In this group of patients this dose resulted in an insignificant fall in renal blood flow and selective pulmonary vasodilatation, but the fall in PVR was small and failed to reach significance. In view of the absence of a fall in mean arterial blood pressure or of any adverse effects a trial of adenosine at higher doses is indicated in this group of patients.

Monoclonal antiplatelet antibody 7E3 (IIb/IIIa receptor blocker) produces rapid reduction in platelet aggregation in humans

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7E3 is a murine monoclonal antiplatelet antibody that is directed against platelet receptor IIb/IIIa. To determine the relation between the dose of 7E3 Fab and inhibition of platelet function a phase I study was performed. Seventy one patients with stable angina were given single doses of 7E3 Fab from 0·1 to 0·3 mg/kg or a loading dose of 0·25–0·3 mg/kg followed by a 0·15 mg/kg/min infusion of 7E3 for 12–36 hours. Platelet function was measured as platelet aggregation (PA) to 20 M ADP, bleeding time (BT), and free IIB/IIIa platelet receptors (FPR). Single doses of 0·1 to 0·3 mg/kg reduced the median PA from 89% to 11% of predose values, increased the median BT from 5 minutes to ≥30 minutes, and reduced median FPR from 50% to 18% of predose values. Continuous infusion caused rapid, sustained inhibition of platelet function for the entire infusion period, with median PA decreased to 10% of predose. Return of BT from ≥40 to ≤12 minutes took 4–12 hours after single dose studies and 6–24 hours after infusion. No significant bleeding or allergic reactions were observed, although low titre human antimurine antibody developed in 16 out of 65 (25%) patients. Therefore, 7E3 Fab produced appreciable inhibition of platelet function at single doses ≥0·25 mg/kg which can be sustained by continuous infusion. This agent may have a role in the management of acute ischaemic events.

Risk stratification in unstable angina: who should be considered for early angiography?

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Chest pain suggestive of acute myocardial infarction remains the most common reason for admission to coronary care units. If myocardial infarction is subsequently excluded, when should such pain be diagnosed as "unstable angina" and who should be considered for early angiography? In a prospective study of all patients admitted to a coronary care unit during one six month period there were 530 cases of chest pain. In 304 acute myocardial infarction was subsequently confirmed, 32 had secondary angina (to an arrhythmia for example), and in a further 14 a specific non-cardiac cause was identified. The remaining 170 patients (180 admissions) were followed up for three years for the development of cardiac events (cardiac death or non-fatal infarction). These events occurred at a constant rate for eight weeks after admission ("early events"), after which the event rate slowed. Patients whose electrocardiogram (ECG) remained normal during their index admission had a benign prognosis whether there was a history of preceding effort angina ($n = 35$) or not ($n = 29$). In this group there were no early events and only a 3% cardiac event rate at three years. An abnormal admission ECG, whether the result of previous infarction ($n = 39$) or with reversible changes ($n = 67$), was associated with a much worse short and long term prognosis (12% events at two months, 32% at three years). After a review of published reports factors reported to be associated with a worse prognosis were studied in an attempt to predict this "at risk" group. The recurrence of pain in hospital, or a cardiac enzyme activity raised to less than twice the upper limit of normal, identified 49 patients in whom 11 of the 13 early events occurred (sensitivity 85%, specificity 59%, positive predictive accuracy 22%). No other prognostic factors, either alone or in combination, gave a similar combination of sensitivity and specificity.

For patients presenting with chest pain in whom a myocardial infarct is subsequently excluded simple, non-invasive risk stratification permits the identification of patients with fundamentally different short and long term prognoses. Recurrent pain or a minor increase in enzyme activity identifies the group most likely to benefit from early revascularisation. These simple criteria would allow physicians in district hospitals to make appropriate use of regional cardiothoracic centres.

Implications of thrombolysis for risk stratification in patients after infarction

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Though the use of thrombolytic agents in acute myocardial infarction (AMI) is associated with an appreciable reduction in mortality, little is known about the effects on life threatening arrhythmic events (sudden death or sustained ventricular tachycardia) and risk stratification. As part of a prospective study at this hospital the effects of thrombolysis on arrhythmic events and risk stratification were investigated. Among 427 serial patients admitted with AMI eligible for thrombolytic treatment, 203 received thrombolysis (group T) and 224 did not (group N). The actuarial probability of life threatening arrhythmic events at two years was appreciably reduced in group T (4·5%) *v* group N (10·6%) ($p = 0{\cdot}001$). Despite treatment with thrombolysis the incidences of arrhythmic markers such as late potentials, ventricular ectopic frequency (> 10/h), impaired ventricular function (< 40%), depressed heart rate variability, and a positive exercise test were similar in both groups. In group N the actuarial probability of arrhythmic events was increased in patients with frequent ventricular ectopic activity (24% *v* 7%, $p = 0{\cdot}008$), positive late potentials (29% *v* 6%, $p = 0{\cdot}001$), impaired heart rate variability (26% *v* 1%, $p = 0{\cdot}001$), and poor left ventricular function (19% *v* 7%, $p = 0{\cdot}02$), but in group T only impaired heart rate variability was associated with an increased probability of arrhythmic events (13% *v* 1%, $p = 0{\cdot}005$).

Thrombolysis reduced the incidence of late arrhythmic events following MI but established methods of risk stratification, particularly those based on long term electrocardiographic recordings and the signal averaged electrocardiogram, may not be applicable in patients given thrombolysis.

Prognostic value of ambulatory ST segment monitoring after acute myocardial infarction

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We have assessed the prognostic value of ambulatory ST segment monitoring (early (6 days, $n = 201$) and late (38 days, $n = 177$)) in 203 patients with acute myocardial infarction when compared with clinical factors, coronary prognostic indices, exercise testing ($n = 174$), and radionuclide ventriculography ($n = 134$). The 29 patients (14%) with ST depression (STD) on early monitoring had more ($p < 0{\cdot}001$) cardiac events (death, reinfarction, or coronary revascularisation) (13/29 (45%)) than those without STD (30/172 (17%)) and events were most common in those patients with three or more STD episodes a day (11/17 (65%) *v* 2/12 (17%), $p < 0{\cdot}03$) or a maximum of at least 1·3 mm STD (10/15 (67%) *v* 3/14 (21%), $p < 0{\cdot}05$). However, patients (56/177 (32%)) who developed STD on late monitoring experienced an increase in cardiac events only when they had three or more STD episodes a day (10/31 (32%) *v* 18/146 (12%), $p < 0{\cdot}01$), at least 20 minutes of STD a day (8/25 (32%) *v* 20/152 (13%), $p < 0{\cdot}05$), or a maximum STD of 1·6 mm or greater (8/25 (32%) *v* 30/152 (13%), $p < 0{\cdot}05$). Furthermore, ambulatory monitoring had superior predictive value to clinical factors, coronary prognostic indices, and left ventriculography but similar prognostic value to exercise testing.

Thus, any STD on ambulatory monitoring early after myocardial infarction identifies patients who are at increased risk whereas STD later carries prognostic value only when it is prolonged, pronounced, or frequent. Ambulatory monitoring may be a useful alternative to exercise testing for identifying patients after myocardial infarction who might benefit from early coronary angiography.

Prognostic significance of heart rate variability in myocardial infarction

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Heart rate variability in the early phase of myocardial infarction reflects cardiac autonomic balance and may carry prognostic significance. We studied heart rate variability in 34 patients with anterior and 36 patients with inferior myocardial infarction by Holter tape recording during the first day of hospital admission. By excluding the RR intervals with lengths outside 20% of the previous cycle to avoid ectopics and sensing artefacts, the following calculations were made in order to express heart rate variability: (*a*) mean RR interval; (*b*) standard deviation of the mean RR interval (SD); (*c*) standard deviation of the mean difference of each RR interval from the preceding one (SDdif). These parameters were calculated for all patients during a four hour night time period (0100–0500). The presence of heart failure and the use of β blockers was similar in the two groups at the time of the recording. Patients with anterior infarction when compared with those with inferior infarction showed a shorter mean RR interval (743 (SEM) (22) *v* 849 (20) ms; $p = 0{\cdot}001$), a smaller SD (39·6 (3·1) *v* 66·2 (4·6) ms; $p < 0{\cdot}001$), and a smaller SDdif (19·8 (1·4) *v* 33·4 (3·4) ms, $p = 0{\cdot}001$). During the hospital stay subsequent heart failure or death occurred more frequently in those patients with low heart rate variability (SD below the median value of 50 ms) (44% *v* 8%; $p < 0{\cdot}01$) independently of infarct site. Low SD had 83% sensitivity and 63% specificity whereas low SDdif (below 23 ms) had 61% sensitivity and 52% specificity in predicting a worse clinical outcome.

These data show that there is a difference in heart rate variability between anterior and inferior myocardial infarction which may reflect the differences in autonomic balance during the early phase of infarction; low variability independently of infarct site is associated with a complicated course.

Evaluation of patient benefit and resource use after early treatment of myocardial infarction with heparin and recombinant tissue type plasminogen activator (Actilyse): study of heparin and Actilyse processed electronically (SHAPE)

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A total of 758 patients with suspected acute myocardial infarction admitted to 32 general hospitals were considered for inclusion in a double blind study comparing recombinant tissue-type plasminogen activator (rt-PA) 100 mg plus heparin with placebo plus heparin. The usual standard treatment for each hospital was continued normally. The original intent was to recruit some 3000 patients but the trial had to be halted prematurely on ethical grounds. The patient data were collected by using records on a personal computer linked by modem to a central site. In all, 164 patients were excluded from the main analysis. Of the 594 patients who satisfied the entry criteria by a 3:1 allocation ratio, 435 were randomly allocated to rt-Pa and 159 to placebo. The primary assessment of patient benefit was measured with the New York Heart Association functional classification. The benefit was measured over the 12 months from treatment and compared with the assessment before admission. There was no statistical difference found between the two groups. Other indices of patient benefit were also examined and no difference was found. Twelve per cent of patients given rt-PA had a bleeding complication compared with 3% given placebo. The incidence of stroke was very low in both groups. There was little difference in the use of resources either in the initial length of hospital stay or in the subsequent need for readmission, angiography, angioplasty, or bypass surgery. There was no difference in the proportion of patients who returned to work between the placebo or the treatment group. Death was not a primary end point. There was some survival benefit for the rt-PA group, although it did not reach significance.

Relations between heart rate, ischaemia, and drug treatment during daily life in patients with coronary artery disease

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Previous studies have shown that little if any increase in heart rate occurs one minute before the onset of ischaemia in ambulant patients with coronary artery disease (CAD). This study has tested the hypothesis that there are characteristic relations between heart rate and ischaemia in ambulant patients with CAD. Twenty one patients with proved coronary disease had 212 episodes of ischaemia during 504 hours of continuous electrocardiographic monitoring. An important increase in heart rate (74 (11) to 95 (14) beats/minute, $p < 0.001$) occurred between five and 30 minutes before the onset of ischaemia. A significantly higher heart rate at onset of ischaemia was seen during Bruce protocol exercise testing than during daily life (117 (12) *v* 90 (15) beats/minute, $p < 0.01$). However, when a less strenuous but more prolonged exercise protocol was used in a subgroup of patients ($n = 12$) ischaemia occurred at a heart rate that was significantly lower than during the Bruce protocol (88 (14) *v* 103 (15) beats/minute, $p < 0.05$) and was not significantly different from the threshold heart rate at onset of ischaemia during daily life (88 (14) *v* 84 (12) beats/minute, NS). As part of two placebo controlled trials, treatment with both propranolol and glyceryl trinitrate altered the distribution of ischaemic events by heart rate, but in opposite directions. Though propranolol largely eliminated events occurring at high (> 100 beats/minute and moderate (80–100 beats/minute) heart rates, the number of events at low (< 80 beats/minute) heart rates was increased. In contrast, glyceryl trinitrate reduced episodes at low and moderate heart rates only.

Important increases in heart rate occur before the onset of ischaemia during daily life but this increase occurs much earlier than has been reported. Duration of heart rate increase seems to influence the heart rate threshold for ischaemia, and this may contribute to the occurrence of ischaemia at lower heart rates during daily life than during exercise testing. Finally, different classes of drugs have characteristic effects on ischaemia occurring at different heart rates.

Inhibition and summation in human heart by long duration subthreshold conditioning pulses

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Inhibition (prolongation of refractoriness) and summation (shortening of refractoriness) have previously been reported to a limited extent in human myocardium by using bipolar conditioning stimuli of conventional (2 ms) pulse width. In 32 patients undergoing clinical electrophysiological studies we studied the effect of long duration, constant current subthreshold pulses on atrial ($n = 22$) and ventricular ($n = 10$) refractory periods. Continuous atrial or ventricular pacing (S1S1 = 500–600 ms) was performed throughout to minimise variability in refractoriness. Effective refractory period (ERP) was determined with a 2 ms pulse at an amplitude of twice the late diastolic threshold (LDT). A long duration conditioning pulse (Sc; duration = S1S2) was introduced. Initial Sc amplitude was 10% of LDT; amplitude and duration of Sc were varied stepwise and the effect on Sc observed. Inhibition was observed in all patients, the atrial ERP being prolonged by a mean of 98% from 238 (SD43) ms to 470 (100) ms with an Sc of mean amplitude 55% of LDT. In 10 patients reversal of the polarity of Sc resulted in shortening of the ERP (summation) by a mean of 27%, from 208 (24) ms to 151 (22) ms. Similar results were produced by ventricular stimulation (ERP was prolonged in all patients, from 239 (36) ms to 475 (88) ms, and shortened in five patients, from 259 (25) ms to 200 (12) ms). With unipolar stimulation cathodal current always produced inhibition; summation, when it occurred, was produced by anodal current.

Inhibition and summation may be produced in the same heart by reversal of stimulus polarity. Long duration current pulses can produce much greater degrees of inhibition and summation than conventional pulses.

Double blind comparison of DDI, DDI with rate hysteresis, VVI, and VVI with rate hysteresis in control of symptoms in carotid sinus syndrome

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DVI pacing has been shown to be superior to VVI pacing in controlling symptoms in the carotid sinus syndrome (CSS). DDI pacing with rate-hysteresis (H) provides the opportunity of physiological pacing at high rate during attacks without the disadvantage of undue pacing every time the rate goes below the programmed rate as in pacing without H. This study was designed to perform a double blind comparison of the efficacy of DDI with H(DDI-H, programmed rate 80, H rate 40), DDI at 60 ppm, VVI with H (VVI-H, programmed rate 80, H rate 40) and VVI 60 ppm. Seventeen patients who had had pacemakers implanted 28·9 (27) months before for the carotid sinus syndrome syncope and pre-syncope were considered for the study. Preinclusion evaluation comprised carotid sinus massage (CSM), supine blood pressure and blood pressure five minutes after 80° tilt, retrograde atrioventricular conduction with and without carotid sinus massage, and DDI pacing during carotid sinus massage to identify patients with vasodepressor component. Two patients were excluded because of negative carotid sinus massage and one patient for marked sinus bradycardia. Fourteen patients, mean age 72·7 (8·8) years (two women), were included in the study and were randomised in a double blind fashion to one of the pacing modes for a period of six weeks each. During these periods they kept a record of episodes of mild dizziness, presyncope, syncope, palpitations, and shortness of breath in a diary. Thirteen patients completed the study; one patient withdrew because of hypertensive stroke. Total number of symptomatic episodes were: (*a*) DDI-H mode mild dizziness 70, presyncope 9, syncope 0, palpitations 16, shortness of breath 38; (*b*) DDI mode mild dizziness 46, presyncope 22, syncope 1, palpitations 36, shortness of breath 65; (*c*) VVI-H mode mild dizziness 62, presyncope 36, syncope 3, palpitations 76, shortness of breath 86; and (*d*) VVI mode mild dizziness 78, presyncope 20, syncope 0, palpitations 84, shortness of breath 61. One patient could not tolerate VVI pacing and had to have the next mode within two days and another patient developed atrial fibrillation in the final pacing mode (VVI-H). Overall the least symptomatic mode of pacing was DDI-H ($p < 0{\cdot}001$).

It is concluded that DDI-H is the best mode of pacing for symptomatic carotid sinus syndrome and is now our pacing mode of choice.

"Subclinical" pacemaker syndrome: randomised study of "symptomless" patients with VVI pacemakers upgraded to dual chamber devices

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Sixteen patients aged 41–84 (69% men) who had had long term pacing for more than three years in VVI mode and had no evidence of the pacemaker syndrome had their pacemakers upgraded to DDD devices during routine generator change. Assessment was before (VVI pre) and after upgrade in three pacing modes (VVI post, DDI, and DDD) in a randomised double blind crossover design. Patients with chronic atrial fibrillation or the pacemaker syndrome were excluded. Subjective, clinical, objective (stress tests), radiographic (chest *x* ray film), and echocardiographic (M mode, cross sectional, colour flow, and continuous wave Doppler echocardiography) assessments were undertaken after four weeks of out of hospital activity in each mode. Perceived general wellbeing and exercise tolerance was better in DDD mode than in VVI pre or post or in DDI ($p < 0{\cdot}01$). Symptoms were less in DDD mode ($p < 0{\cdot}05$). After study completion 75% preferred DDD and 12% DDI and the remainder had no preference. Seventy two per cent found VVI post least acceptable whereas none found DDD least acceptable. Treadmill exercise tolerance was greatest in DDD mode ($p < 0{\cdot}001$) but did not differ in the remaining modes. Chamber dimensions (echocardiography) and cardiothoracic ratio (chest *x* ray film) did not differ in any mode. Improved cardiac output was seen at rest in DDD mode ($p = 0{\cdot}03$) compared with VVI pre and post modes but not DDI mode. Mitral and tricuspid regurgitation was least in DDD mode but did not correlate with symptoms.

Thus patients who are receiving optimal pacing in VVI mode benefit subjectively and objectively from upgrade to DDD mode whereas DDI has little effect. This suggests the existence of a "subclinical" pacemaker syndrome that becomes apparent only when physiological pacing is introduced.

Physician implanted defibrillator: first clinical experience of a new transvenous device

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A pacemaker/cardioverter/defibrillator was implanted without a thoracotomy in three male patients with a history of drug resistant ventricular tachycardia and sudden cardiac death. This new device utilises two pace/sense/defibrillate electrodes positioned via the subclavian vein in the right atrial appendage and in the right ventricular apex. A monophasic bidirectional shock is delivered between these and a subcutaneous axillary patch. The generator is situated in an abdominal pocket. Implantation took between 2·5 and 4 hours and was performed under general anaesthesia. *x* Ray screening was required for between 5 and 35 minutes. During intraoperative testing there was a loss of sensing and pacing postshock in two patients. This was corrected by repositioning the right ventricular electrode (total five minutes). A good defibrillation threshold was achieved in all patients (10 J, 10 J, 20 J) and was maintained at the one month follow up. The implant procedure was uncomplicated and patients were fit for discharge two days after operation. In one patient a lead complication required repositioning after one week.

The implantation of a transvenous defibrillator is a safe and effective alternative to the standard thoracotomy approach.

Prophylactic use of implantable cardioverter defibrillator after myocardial infarction: predicting cost in high and low risk patients

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Interest is growing in the prophylactic use of the implantable cardioverter defibrillator (ICD) in patients at high risk of sudden death. We costed ICD use in myocardial infarction survivors by using data from our post-myocardial infarction database of 525 patients. All cause cumulative mortality after one year (Y1) was 8·4%, after two years (Y2) 11·5%, and after three years (Y3) 13·7%. Sudden death mortality was 3·8% (Y1), 4·5% (Y2), and 4·5% (Y3). Patients at higher risk could be identified. In the group with left ventricular ejection fraction <40% (EF < 40) (n = 201) mortality from sudden death was 7·5% (Y1), 7·5% (Y2), and 7·5% (Y3) while a combination of reduced heart rate variability, > 10 ventricular ectopics per hour, and positive late potentials (n = 25) identified a group (HRG) with sudden death mortalities of 22·8% (Y1), 29·9% (Y2), and 29·9% (Y3). We costed the use of the ICD in all patients and in groups EF < 40 and HRG over a three year period assuming an ICD life of three years, 100% prevention of sudden death, no antiarrhythmic drug treatment, and transthoracic implantation. Costs are ICD and patches (£10 700), surgery (£3000), extra seven days as an inpatient (£1400), outpatient follow up over three years (£1400). Total implant and follow up cost was £16 500. Screening costs were £50 (EF < 40 group) and £130 (HRG group) per patient screened. Implantation in all patients saved 2·73 life years per 100 implants (LY%) at a cost per life year of £604 000. In the EF < 40 group the ICD saved 10·7 LY% at a cost of £155 500 per life year. In the HRG group (in which 33% of all sudden death occurs) the ICD saved 58·3 LY% at a much reduced cost of £33 000 per life year but was still expensive when compared with other accepted invasive treatment.

Pending a reduction in this cost by improved selection of patients at high risk of sudden death, there is no general indication to implant an ICD in high risk patients after myocardial infarction but a limited trial to clarify the true costs may be justified.

Anatomical problems associated with implantation of cardioverter defibrillator

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A Guardian cardioverter defibrillator (ICD) was implanted in nine patients, all men (mean age 60 (6) years, range 50–69), over a 15 month period. Three patients (33%) suffered out of hospital ventricular fibrillation, one (11%) had exercise induced ventricular fibrillation and two (22%) exercise induced ventricular tachycardia, and three had haemodynamically unstable ventricular tachycardia. During the first implantation severe postoperative bleeding occurred with suturing of the epicardial patches, and all subsequent patches were stitched to the parietal pericardium. In one patient the generator eroded through the rectus sheath, was repositioned within the thorax, where it also eroded, and was subsequently explanted. In a further case the generator was electively implanted in the thorax because of restricted space in the rectus sheath and for the same reason in another patient the generator was sutured anteriorly to the sheath. During a mean follow up of 11 months (3–17) there were seven inappropriate shocks, three during atrial flutter (one patient) and four due to lead fracture (two patients). There were no deaths.

In this series a common problem was related to the size of the ICD generator precluding its implantion in the rectus sheath. This was overcome by repositioning in other body cavities. The use of an ICD is associated with treatable morbidity but there were no deaths in this follow up period.

Physiological properties of human hypertrophic myocardium and impaired contractility

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Hypertrophy may be associated with changes in inotropy, intracellular pH (pH_i), and sodium concentration ($[Na^+]_i$). Strips of human left ventricle removed at valve replacement were perfused with Tyrode's solution (pH 7·35 in 5% carbon dioxide and 95% oxygen at 37 °C) and stimulated at 1 Hz and isometric twitch (T) and mechanical restitution curves (MRC) analysed. pH_i and $[Na^+]_i$ were measured by using ion selective electrodes in quiescent preparations. Tension was reduced in pressure overloaded myocardium (0·72 kN/kg (n = 20) *v* controls, 1·72 (n = 15); p < 0·05) and negatively correlated with cell diameter (R = −0·66, p = 0·02 (n = 11)). MRC time constants (t_1, t_3) correlated with cell diameter (t_1 R = 0·62, t_3 R = 0·81 (n = 11)). Mean pH_i was 7·27 (SD 0·19) ((n = 7) mean pH_e 7·42) and $[Na^+]_i$ was 13·31 (SD 4·13) μmol^{-1} (n = 6). $[Na^+]_i$ correlated with cell diameter (R = 0·98, p = 0·02). Reducing extracellular pH (pH_e), by raising carbon dioxide content, led to the largest fall in tension (% control T/unit pH_e) in volume overloaded myocardium (108% (n = 15) *v* controls, 73% (n = 9) p = 0·05). In pressure overloaded myocardium T/pH_e was inversely related to hypertrophy on electrocardiographic voltage criteria (R = 0·52, p = 0·03 (n = 18)). In resting muscle pH_i correlated with pH_e and buffering capacity "pH_i/pH_e" correlated with T/pH_e slopes of contracting muscle.

It is proposed that altered homoeostasis of pH_i and $[Na^+]_i$ in hypertrophy could explain abnormalities of contractility.

Platelet and white cell accumulation in early infarction

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Both white cells and platelets have been implicated as contributing to myocardial damage after infarction. In nine pigs (20–39 kg) the left anterior descending coronary artery (LAD) was occluded and the area of myocardium at risk determined by intravenous thallium–201, given five minutes after the occlusion. Autologous white cells were labelled with technetium–99m and platelets with indium–111 and reinjected before occlusion. The animals died or were sacrificed at a mean time of 85 minutes (12–120 minutes) and the hearts were extracted, opened, and laid flat on a γ camera and imaged to determine the area at risk and the relative distribution of labelled platelets and white cells. Paired blocks of myocardium were taken from the centre of the infarct area, just below the LAD tie (ischaemic area), and two normal areas and each block was subdivided into three for γ counting. Indium labelled platelets seemed to be evenly distributed throughout the myocardium, with similar distribution in the infarct and ischaemic and normal myocardium (corrected for flow ratios 0·7, 0·9, and 1·0). Technetium labelled white cells were increased within infarcted (227% (43·2)) and ischaemic myocardium (200·92% (35·5)) compared with normal (100·4% (25·7)) myocardium, which when corrected for flow resulted in a substantial increased accumulation of white cells in the infarct (ratio 17·0 (3·24)) and ischaemic myocardium (4·0 (1·06)) compared with normal myocardium (1·0 (0·20)).

These results provide evidence of early white cell accumulation in infarcted and ischaemic myocardium.

Glucose tolerance test and insulin concentrations in British Asian and white patients and in Asian patients in India with coronary artery disease

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Blood glucose and insulin concentrations were measured 0, 1, and 2 hours after a 75 g oral glucose challenge in a consecutive series of 56 British Asian (BA) and 65 randomly selected white patients (WP). These were compared with 47 BA and 57 white controls (WC) randomly sampled from the community. A consecutive series of 28 patients in India were compared with 28 randomly selected controls, measurements for these subjects being at 0 and 2 hours. All patients had angiographically confirmed coronary artery disease. Most BA subjects had migrated from the north west of the Indian subcontinent, and subjects resident in India were from the same geographical area. These groups have not been previously compared. Significance was set at a conventional 5% level. Impaired glucose tolerance and overt diabetes were significantly more common in BA and Asians in India (AI) than in white subjects—that is, 40·7%, 46·4%, and 18% respectively. This was more common in patients than in controls—namely, 24·6% *v* 10·5% in white subjects, 42·8% *v* 38·2% in BA, and 57·1% *v* 35·7% in AI. Serum glucose concentration at 0 hours was borderline significantly higher for WP than controls but was very significantly higher in BA and AI patients than controls—5·0 *v* 4·6, 5·6 *v* 5 0, and 5·5 *v* 5·1 respectively. At one hour BA patients had significantly higher values than controls (10·0 *v* 8·5) unlike white patients (7·5 *v* 7·6). At 2 hours values were only borderline significantly higher in WP than WC (5·8 *v* 5·1) but very significantly higher in BA (7·3 *v* 6·1) and AI patients (8·2 *v* 7·4). The geometric mean of insulin concentrations was significantly higher in patients than in controls in all the groups at 0, 1, and 2 hours—13 *v* 7, 78 *v* 55, and 47 *v* 28 for white subjects; 23 *v* 16, 107 *v* 96, and 70 *v* 52 for BA; and 18 *v* 14, 70 *v* 48 for AI at 0 and 2 hours. These concentrations were significantly higher at all times in Asians than in white subjects both patients and controls.

We conclude that impaired glucose tolerance and diabetes is significantly more common in Asians than in white subjects and more so in AI. Insulin resistance is seen not only in Asian patients but also in white patients, with significant hyperinsuliaemia also found in Asian controls as compared with white controls.

Apolipoprotein (a) concentrations and susceptibility to coronary artery disease in patients with peripheral vascular disease

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Patients undergoing surgery for peripheral vascular diseases often have generalised atherosclerosis and a high incidence of significant coronary artery disease. Apolipoprotein (a) (Apo(a)) concentrations are genetically determined and have been strongly associated with the presence of coronary artery disease in the general population. The close structural homology that has been shown between Apo(a) and plasminogen has been suggested as an important link between lipoprotein metabolism, the clotting or fibrinolytic system, and susceptibility to coronary artery disease. The aim of this study was at establishing whether an association exists between Apo(a) concentrations and coronary artery disease in patients with atherosclerotic peripheral vascular disease. We studied 38 consecutive patients under consideration for peripheral vascular surgery, all of whom underwent clinical assessment and coronary arteriography. A serum sample from each patient after fasting was analysed for concentrations of total cholesterol, high density lipoprotein cholesterol (HDLC), Apo(a), apoprotein A-I (Apo A-I), apoprotein B (Apo B), and triglyceride. Apo(a) was measured by a two site immunoradiometric assay using monoclonal antibodies to two different epitopes of Apo(a) (Pharmacia Diagnostics AB). The within assay coefficient of variation was 3·8%. Of the 38 patients, 27 had significant coronary artery disease while 11 did not. These two patient groups were of similar age and sex distribution and had similar patterns of peripheral vascular disease and smokiing habits. None of the patients had diabetes mellitus, but a history of hypertension was found more frequently in patients with coronary artery disease (χ^2, p < 0 01). Apo(a) concentrations were significantly greater in patients with coronary artery disease (median 328 U/l (range 33–1638) *v* 122 U/l (19–206), p < 0·002) (Mann–Whitney U test)) whereas HDLC concentrations were significantly lower in this group (mean 0·97 (SD 0·22) *v* 1·25 (0·49), p < 0·05 (unpaired *t* test)). No significant difference was observed in the distribution of total cholesterol, Apo A–I, Apo B, or tryglyceride between the two groups.

Thus, we conclude that high concentrations of Apo(a) and low concentrations of HDLC are significantly associated with the presence of coronary artery disease in patients with surgically correctable peripheral vascular disease. Measurement of Apo(a) concentrations may prove to be a useful additional discriminator in the detection of patients with coronary artery disease within this group.

Free radical production during human myocardial reperfusion

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Oxygen free radical production has been shown during myocardial reperfusion in animal models. Peak radical detection in the coronary sinus occurs 2–5 minutes after reperfusion, thus excluding confusion with ischaemic washout (5–15 seconds). We studied free radical activity in the blood of 15 patients undergoing percutaneous transluminal angioplasty to proximal anterior descending lesions with the highly specific technique of electron spin resonance spin trapping. Sequential coronary sinus sampling alone was performed in 10 patients and in a further five patients paired aortic and sinus samples were obtained. Phenylbutylnitrone was used to spin trap free radicals present in the blood and the samples were then evaluated by electron spin resonance. In nine of the 15 patients free radical activity was detected in the coronary sinus blood, with peak detection frequency between 2 and 4 minutes after balloon deflation. Radicals were not detected in any of the aortic samples or in the coronary sinus samples taken before and during balloon inflation.

This study provides the first unequivocal evidence of free radical production during human myocardial reperfusion.

Dissociation between angiographic findings and functional assessment of myocardial ischaemia soon after successful coronary angioplasty

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To understand better the mechanism responsible for exercise induced myocardial ischaemia after sucessful coronary angioplasty (PTCA), 13 patients who underwent single vessel PTCA were studied. Exercise testing was performed before and on day 7 after PTCA, which was repeated after 10 mg sublingual isosorbide dinitrates if the test gave positive results. Quantitative coronary arteriography was also performed on day 8 after PTCA in the basal state (B), after intracoronary infusion of 0·9% saline and 1, 5, 10, 20 μg ergometrine, and after 300 μg glyceryl trinitrate (GTN). All antianginal drugs except for aspirin were stopped 48 hours before both phases of the study. All patients had a positive exercise test (≥1 mm ST segment depression) before PTCA but on day 7 seven patients had a positive exercise test with chest pain (group 1) and six patients had a negative exercise test (group 2). In group 1 all positive exercise tests on day 8 became negative when repeated after nitrates. There was no significant difference in the basal luminal diameter before, immediately after, and eight days after PTCA between the two groups. Intracoronary ergometrine was associated with a dose dependent constriction of the angioplastied segment with no significant difference in the magnitude of the response between the two groups (maximum constriction for group 1 was 19% (3) ($p < 0·001$ *v* B) and in group 2 was 20% (4%) ($p < 0·006$ *v* B)). No angina, ischaemic ST changes, or occlusive or subocclusive spasm occurred in any patient of either group. The degree of dilatation induced by glyceryl trinitrate was also similar in both groups.

Thus, soon after PTCA exercise testing may be positive despite successful dilatation. The lack of hyperreactivity of large epicardial vessels to the powerful vasoconstrictor stimulus of ergometrine indicates that the mechanism responsible for exercise induced myocardial ischaemia after PTCA lies in small coronary vessels, an abnormality amenable to be abolished by glyceryl trinitrate.

Acute effects of transition to a Fontan circulation

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The immediate effects of the Fontan operation on left ventricular function were studied in five patients by using simultaneous high fidelity intraventricular pressure measurements and M mode Doppler epicardial echocardiograms recorded before and after pulmonary bypass. The Fontan operation had no effect on left ventricular end diastolic pressure or systolic pressure or on load dependent indices of ventricular function (shortening fraction, rate of change of dimension, rate of posterior wall thickening, and thinning), but large changes in left ventricular geometry occurred. Maximum cavity dimension fell from 3·6 (0·62) cm to 3·0 (0·68) cm ($p = 0·03$) and minimum dimension fell from 2·7 (0·57) cm to 2·3 (0·05) cm ($p = 0·046$). Maximum posterior wall thickness increased from 11 (3·6) mm to 14 (2·1) mm ($p = 0·026$) and minimum posterior wall thickness increased from 7·1 (3·6) mm to 10·4 (1·5) mm ($p = 0·003$). Doppler echocardiography with simultaneous intraventricular pressure measurement showed gross isovolumic intraventricular flow suggestive of incoordinate wall motion in all patients.

The Fontan operation causes a sudden reduction in left ventricular preload, which in the presence of a maintained shortening fraction leads to a "hypertrophic" and incoordinate left ventricle.

Left ventricular dysynchrony after the Fontan operation: evidence for incoordinate systolic and diastolic wall motion

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Thirty patients were studied between one day and six years after the Fontan procedure (FP) for evidence of regional abnormalities of ventricular wall motion. Left ventriculograms from 14 patients after FP and 11 patients with univentricular atrioventricular connection before FP were digitised frame by frame. Strict criteria for incoordinate wall motion were used (outward movement of >50% of total outward movement of four adjacent segments before mitral valve opening or inward movement of >50% of total inward movement in four adjacent segments after minimum cavity dimension) so that minor abnormalities were not included. There were major abnormalities of regional wall motion in 12 of the 14 patients after FP but in only three of the 11 patients before surgery. Doppler inflow velocities were recorded in 16 patients with simultaneous phonocardiogram and echocardiogram. Abnormal systolic base to apex flow reflecting incoordinate contraction was detected in 15 patients. This had a mean velocity of 23 cm/s (16–34) and lasted for 65% (40–83%) of the total electromechanical systole. Abnormal intraventricular flow from base to apex during isovolumic relaxation was detected in 11 patients with a mean velocity of 19 cm/s (10–27). These abnormal flow transients were not detected in any of the 10 normal children or six patients with a univentricular atrioventricular connection before FP.

Major abnormalities of regional ventricular motion, which may have important implications for global ventricular function and efficiency, are common after FP.

Transoesophageal echocardiography: new diagnostic technique in evaluation and follow up of Fontan procedures

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Transoesophageal echocardiography (TOE) was used prospectively in 18 patients (aged 1·6–34 years; mean 12·6 years) to determine whether this technique may be superior to transthoracic echocardiography (TTE) in the assessment of the immediate (five patients) or intermediate results (13 patients) after a wide range of Fontan type procedures. The findings were correlated with one another and cardiac catheterisation (11 patients). Atrial shunting was documented by TOE in three patients and by TTE in only one. Two had this subsequently confirmed by cardiac catheterisation; the third underwent reoperation based on the TOE study alone. Right atrial thrombus formation was detected by TOE in three patients and by TTE in one patient. Repeat TOE studies were used to evaluate thrombolytic treatment in two, which was successful in one. Spontaneous right atrial contrast was identified in an additional two patients only by TOE. Atrioventricular valve regurgitation (11/18) was better defined by TOE than by TTE studies (5/18). A coronary artery fistula was identified by TOE in two patients and by TTE in none. Of the total of 29 Fontan and Glenn connections established in these 18 patients, 25 (86%) were able to be evaluated by TOE and only 14 (48%) by TTE. Posterior Fontan connections were able to be evaluated by TOE in 10/10 patients (TTE 5/10), and Glenn shunts in 8/9 patients (TTE in 3/9). Anterior Fontan connections were better shown by TTE (6/8 patients) than by TOE (5/8). Pulmonary artery obstruction was documented by TOE in three patients and by TTE in one. This was confirmed by subsequent cardiac catheterisation in all three and was excluded in the remaining eight patients who had catheterisation. Transoesophageal pulsed wave Doppler interrogation of pulmonary artery and pulmonary vein flow patterns consistently allowed a detailed evaluation of the Fontan circulation. Whereas pulmonary artery flow patterns varied according to the procedure used, the corresponding pulmonary vein flow patterns were found to be independent of the type of Fontan connection used.

TOE is an important diagnostic and monitoring technique in patients requiring Fontan procedures. In this series it proved to be largely superior to TTE and of substantial additional value to cardiac catheterisation. Pulsed wave Doppler studies allow a detailed evaluation of haemodynamic characteristics after different types of Fontan procedures.

Management of pulmonary artery stenosis after arterial switch operation for transposition of the great arteries

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The arterial switch operation is the treatment of choice for transposition of the great arteries and is now performed with a low mortality. One of the recognised complications is pulmonary artery stenosis (PAS), and we have found this in 16 out of 84 survivors. The following differences were observed between those infants with PAS and those without (NPAS). The mean age at operation of the PAS group was 14·8 (SD 11·2) days and for NPAS 271 (1085) days (p = 0·05). The mean period of ventilation for PAS was 3·8 (29) days and for NPAS 2·5 (1·9) days (p = 0·04). The mean time taking intravenous inotropic drugs for infants with PAS was 5·06 (SD 3·3) days and for those without 3·1 (1·8) days (p = 0·002). The mean postoperative Doppler velocity was 3·13 (0·9) m/s for PAS. Twelve infants underwent cardiac catheterisation at a mean of 252 (185) days after surgery and six had balloon dilatation. Of those with PAS at the anastomosis site, four out of five had successful dilatation, and of those with PAS at the origin of the branch pulmonary arteries, four out of six had successful dilatations. None of the three patients with long segment PAS had successful dilatation. Six patients proceeded to surgery. There were no complications and only one restenosis occurred after reoperation, which was dilated successfully.

We suggest a risk factor for the PAS group is a younger age at surgery and they are more likely to require prolonged postoperative ventilation or inotropic support. Balloon dilatation should be undertaken for main or branch origin stenosis. Balloon dilatation or surgery is safe and effective.

Abnormal right ventricular diastolic function is common after relief of severe outflow tract obstruction

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With Doppler echocardiography and simultaneous respirometry and electrocardiography right ventricular diastolic function was studied in seven symptom free patients at a median interval of five years after complete correction of pulmonary atresia with intact septum (three) or critical pulmonary stenosis (four) and in seven age and sex matched controls. Tricuspid and pulmonary flow velocities were measured, and the atrial contribution to forward flow in the pulmonary artery was assessed with planimetry. Three inspiratory and three expiratory cardiac cycles were analysed and averaged. Relief of right ventricular outflow tract obstruction was complete in all patients. All, however, continued to show evidence of right ventricular diastolic abnormalities. There was obvious forward flow in the pulmonary artery coincident with atrial systole, which accounted for 23% (6·7–42%) of the total pulmonary flow in the patient group. This was not detected in controls. Though mean tricuspid E wave deceleration and E/A ratio was similar in patients and controls, a significant decrease in E wave deceleration time was observed in the patient group during inspiration (p = 0·008).

Even after complete relief of right ventricular outflow tract obstruction in infancy abnormalities of right ventricular diastolic function, characteristic of a restrictive process (prominent atrial contribution to pulmonary flow and a shortening in tricuspid E wave deceleration during inspiration), are common even in symptom free patients.

Congenital heart disease: nutritional state of children undergoing cardiac surgery

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Nutritional state is a major determinant of the magnitude of the metabolic response to injury, malnutrition being associated with poor wound healing, reduced immunity, and impaired respiratory function. We are currently studying the energy requirements of children with congenital heart disease before and after surgery by the doubly labelled water technique; as a preliminary we investigated their preoperative nutritional state. Forty children and 29 variables were studied (19 males, 21 females, mean age 1·75 years, range 2 days to 4·77 years). Body weight was less than or equal to the 10th centile in three and to the third centile in 15 (37·5%). Results for height were (respectively) 1 and 8 (20%) and for triceps and subscapular skinfold thickness 6 and 3 (7·5%) and 4 and 6 (15%). Bicarbonate concentrations were low in 18; chloride was raised in 29. Total protein and albumin concentrations were subnormal in 13 and in 19 (47 5%) respectively. Transferrin was low in five (12·5%), zinc in seven (17 5%), copper in four, and magnesium in one. Phosphate was raised in 26, calcium in 11, aspartate transaminase activity in nine, alanine transaminase activity in two, and bilirubin in two. C reactive protein was raised above 10 mg/l in three patients; urinary 3-methylhistidine (a marker of whole body protein breakdown) was raised in these and in five others (20%). Overall, in 60% of patients the values of seven or more variables were abnormal.

These results support the clinical impression that many children undergoing cardiac surgery are severely undernourished. This is in contrast to previously reported findings in adults.

Early use of captopril limits left ventricular remodelling after myocardial infarction

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Captopril treatment started one to three weeks after myocardial infarction may limit left ventricular remodelling. Angiotensin II concentrations peak within a few days of infarction and the earlier use of captopril may be advantageous. In a double blind study 99 patients (82 men, age range 40–75) were randomly assigned to treatment with captopril or placebo within 24 hours of myocardial infarction, continuing for one year. No patient had to be withdrawn from captopril treatment because of acute hypotension, and over 12 months withdrawals and deaths were balanced between the treatment groups. Serial cross sectional echocardiography was used to assess ventricular remodelling. After 12 months of treatment left ventricular end diastolic volume index (EDVI) had increased (8·4 (1·9) ml/m^2 in the captopril group *v* 19·0 (2·6) ml/m^2 with placebo, p = 0·002). Left ventricular end systolic volume index (ESVI) increased by 5·4 (1·3) ml/m^2 in the captopril group *v* 14·7 (2·3) ml/m^2 with placebo (p = 0·001). The resulting mean volume indices were significantly lower in the captopril group: EDVI 76·9 (3·0) ml/m^2 *v* 89·5 (3·1) ml/m^2, p = 0·005; ESVI 47·0 (3·8) ml/m^2 *v* 59·9 (3·4) ml/m^2, p = 0·005. In the patients with anterior myocardial infarction, anterior segment length increased by 4 (2) mm in the captopril group *v* 17 (4) mm with placebo (p = 0·009). In the subgroup with inferoposterior myocardial infarction the posterior segment length increased by 4 (2) mm in the captopril group *v* 13 (3) mm with placebo (p = 0·03)

Thus captopril treatment started within 24 hours of myocardial infarction is safe and significantly attenuates ventricular remodelling over one year.

Influence of early vasodilator treatment on myocardial infarct size and the inflammatory response

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To test the hypothesis that captopril and nitrates may reduce infarct size and that captopril may scavenge free radicals or suppress inflammation, we have conducted a double blind randomised study in which 105 patients with acute myocardial infarction were assigned to treatment with placebo (n = 36), isosorbide mononitrate 20 mg three times a day (n = 33), or captopril 12·5 mg three times a day (n = 36). Treatment was started within 24 hours of the onset of pain (mean 14·4 h) and was continued for 28 days. Infarct size was assessed two to four days after the onset of pain by tomographic technetium-99m pyrophosphate imaging. Quantification of infarct size was by voxel counting. Vasodilator treatment had no influence on infarct size (placebo 58·9 (9 0), nitrate 65 8 (5·2), captopril 58·8 (7·8) cm^3). The inflammatory response was quantified by estimating plasma neutrophil elastase activity, a measure of neutrophil activation, and the plasma concentration of the phospholipid diene conjugated isomer of linoleic acid, a product of free radical lipid attack. The average neutrophil elastase activity over the 48 hours after trial entry was similar in the three groups (placebo 40·0 (3·6), nitrate 52·3 (5·5), captopril 41·6 (2·5) ng/ml). There was no evidence of suppression of free radical production with similar values of the ratio of the diene conjugated to the diene unconjugated isomer of linoleic acid over the same time period (placebo 2·8 (0·2), nitrate 2·9 (0·2), captopril 2·9 (0·3) $(\times 10^{-2})$.

We conclude that early oral vasodilator treatment has little or no effect on infarct size or infarct associated inflammation.

One year comparative study of captopril and flosequinan in patients with chronic heart failure

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Two hundred and nine patients with chronic heart failure, whose symptoms remained despite at least 80 mg frusemide daily and who were not taking vasodilators were randomised double blind to either flosequinan or captopril for one year. Before randomisation each patient completed a single blind placebo period until their exercise tolerance had plateaued. The patients were stratified according to whether they were capable of performing at least three minutes of treadmill exercise to either a treadmill group or if they could not to a corridor walk test group. The treadmill group underwent exercise tests at weeks 2, 4, 6, 8, 13, 26, 39, and 52 according to a modified Bruce protocol whereas the walk test group completed a six minute test only at the same times. One hundred and two patients were randomised to flosequinan; 65 were withdrawn, of whom 22 died. Forty three patients were withdrawn from captopril, of whom 17 died. Withdrawal from flosequinan was due to worsening heart failure in 11 and adverse events in 28 whereas the corresponding numbers in the captopril group were nine and 15. In those patients capable of treadmill testing with their last exercise time taken as end point there was no difference in the increase in treadmill exercise time; in the flosequinan group the mean baseline exercise time was 593 s and the end point 709 s ($n = 31$), and in the captopril group the baseline was 572 s and the end point 738 s ($n = 36$) ($p = 0·57$). Values were similar in both groups in the patients who completed the corridor walk test only: the distance walked at baseline was 208 m and at the end point 271 m in the flosequinan group and 252 m and 326 m in the captopril group ($p = 0·71$). Analysis of the exercise times at each visit for those patients who continued in the study also showed no differences.

Flosequinan had equal efficacy with captopril in the patients who were able to continue treatment but it was associated with a greater withdrawal rate, predominantly due to adverse events, over the one year period of this study.

Comparison of a new neutral endopeptidase inhibitor with frusemide in left ventricular dysfunction

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Atrial natriuretic factor has significant diuretic and vasodilatory properties and is degraded by neutral endopeptidase. Therefore, a specific inhibitor of this enzyme might have beneficial effects in left ventricular dysfunction by increasing circulating atrial natriuretic factor concentrations. We compared such an inhibitor (candoxatril) with frusemide in 18 patients with previous myocardial infarction. All patients had left ventricular dysfunction, defined as an end diastolic dimension > 55 mm; fractional shortening < 25%; and a reduced exercise capacity with a maximum oxygen consumption of < 25 ml/kg/min. Patients were randomised in single blind fashion to (*a*) candoxatril 200 mg twice a day, (*b*) candoxatril 400 mg twice a day, or (*c*) frusemide 20 mg twice a day. After 10 days atrial natriuretic factor concentrations increased significantly by 155% ($p < 0·05$) and 210% ($p < 0·01$) with candoxatril 200 mg and 400 mg respectively. With frusemide, concentrations decreased by 40% ($p < 0·05$). There was a significant increase of 329% in plasma renin activity with frusemide but no significant change with candoxatril. At four hours after dosing mean pulmonary wedge pressure decreased by 41% from 13·1 to 7·7 mm Hg ($p < 0·05$) and by 45% from 15·5 to 8·5 mm Hg ($p < 0·05$) after candoxatril 200 mg and 400 mg respectively. With frusemide there was a smaller decrease of 15% from 11·5 to 9·8 mm Hg ($p < 0·05$). Similar changes were noted for right atrial pressure recordings. This reduction was sustained by candoxatril at six hours but became attenuated after four hours with frusemide. Mean arterial pressure fell by 10·5 mm Hg ($p < 0·05$), 14·3 mm Hg ($p < 0·01$), and 3·7 mm Hg (NS) with candoxatril 200 mg, candoxatril 400 mg, and frusemide respectively. No significant changes in heart rate or cardiac output were noted. After dosing urine volume increased by 376%, 201%, and 498% over the first three hours and by 337%, 151%, and 270% over the next three hour period for candoxatril 200 mg, candoxatril 400 mg, and frusemide respectively. Sodium excretion was similarly increased by 213%, 236%, and 367% for the first three hour period and by 222%, 233%, and 214% for the second three hours respectively.

Both candoxatril and frusemide lower filling pressures and induce a natriuresis. Candoxatril in contrast to frusemide is not associated with adverse neuroendocrine effects and its haemodynamic effects are more prolonged. Therefore, neutral endopeptidase inhibitors may have advantages over standard diuretic treatment in left ventricular dysfunction.

Decreased overall sympathetic activity during inhibition of angiotensin converting enzyme in patients with chronic heart failure

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Angiotensin converting enzyme inhibitors improve symptoms and survival in chronic heart failure, some of which benefit may be due to improved autonomic balance. We used whole body tritiated noradrenaline (NA) kinetics to evaluate the short (48 hours) and medium term (six weeks) effects of angiotensin converting enzyme inhibition with ramipril on overall sympathetic activity in 21 patients with chronic heart failure (aged 68 (3) years) stabilised by diuretic treatment (69 (6) mg frusemide). At each visit radiotracer NA kinetics (assessed in arterial plasma) were measured at rest and at the same level of supine bicycle exercise. In eight patients given placebo no changes in NA kinetics occurred over the six week treatment period (whole body NA spillover at rest 240 (32), 251 (34), and 230 (18) ng/min/m^2 at baseline and after two and 42 days treatment respectively, NS; NA spillover during submaximal exercise 561 (65), 584 (187), and 619 (96) ng/min/m^2 respectively, NS. Pretreatment values were, however, lower than those in the 13 patients who received ramipril 5–10 mg daily. In the ramipril treated patients there was a decline with treatment in resting and exercise arterial plasma NA concentration (339 (29), 315 (37), and 303 (35) pg/ml at the three time points at rest, $p < 0·05$; 681 (48), 557 (64), and 562 (84) respectively during exercise, $p < 0·05$) and in whole body NA spillover to arterial plasma, both at rest (385 (39), 354 (43), and 312 (32) ng/min/m^2, $p < 0·05$) and during submaximal exercise (733 (46), 728 (114), and 612 (81) ng/min/m^2, $p < 0·05$). This decline was more pronounced at six weeks than at 48 hours. Whole body NA clearance did not change during the treatment period in either group.

Angiotensin converting enzyme inhibition with ramipril in patients with chronic heart failure is associated with a decline in overall sympathetic tone. This effect is more prominent at six weeks than at 48 hours, which may be relevant to the delayed clinical benefit of angiotensin converting enzyme inhibition.

Is routine withdrawal of digoxin necessary before elective cardioversion?

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Digoxin treatment is often withheld before direct current (DC) cardioversion because of the risk of ventricular arrhythmias. To test the necessity for this we randomly allocated 35 patients admitted for DC cardioversion for atrial fibrillation (AF) either to continue taking digoxin (group 1) or to stop treatment for 48 hours (group 2). All patients had continuous electrocardiographic monitoring from one hour before cardioversion until two hours after. Four patients were also taking amiodarone 200 mg once daily, two in group 1 and two in group 2. There were 17 patients in group 1 and 18 in group 2. Mean heart rate was similar before cardioversion (97 beats/min in group 1 *v* 95 beats/min in group 2) and after (83 *v* 85 beats/min), and there was no difference between potassium concentrations in the two groups (4·36 *v* 4·17 mmol/l). Overall success for conversion to sinus rhythm was 60% and 65% in group 1 and 56% in group 2. In group 1 mean digoxin concentration was 1·79 nmol/l (range 1·0–5·4 nmol/l) and in group 2 0·34 nmol/l (0–1·0 nmol/l), which was significantly different from the value in group 1 ($p = < 0{\cdot}001$). There were no sustained ventricular arrhythmias in either group. The mean number of ventricular ectopics in group 1 before DC shock was 80 (0–595) and after was 50 (0–346). The number of ventricular ectopics did not significantly differ in group 2 (50 (0–156) before cardioversion and 77 (0–480) after). There was no correlation between the number of ventricular ectopics and serum digoxin concentrations.

These findings show that withdrawal of digoxin does not influence ventricular ectopy during elective cardioversion and may be unnecessary.

Coronary angiography in Glasgow: relation to coronary heart disease and social class

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Standardised mortality ratio (SMR) for coronary heart disease correlates highly with social deprivation score (SDS). We examined their influence on coronary angiography rates in 1986 and 1987 in Greater Glasgow Health Board residents aged 35–64. SDS for each patient was derived from SCOTDEP scores (range 1 to 7—low to high SDS) from area postal codes. Coronary angiography rates were obtained from OPCS 3 code 306·9. SMRs in men were 52, 72, 88, 107, 120, 133, and 128 for SDS 1–7 respectively. Mean angiography rate a year and number performed a year were 4·5 per 1000 and 692. When adjusted for the different SMR, used as the criterion of need for angiography, predicted rates were 2·3, 3·2, 3·9, 4·8, 5·3, 5·9, and 5·7 per 1000 for SDS 1–7 respectively. Observed rates were 3·6, 4 5, 4·7, 4·5, 5·2, 5·1, and 4·1 per 1000 for SDS 1–7 (excess 33, deficit 46 angiograms a year (155% and 72% of predicted) for comparable sized SDS 1 *v* 7). SMRs in women were 38, 65, 73, 102, 96, 141, and 144 for SDS 1–7 respectively. Mean angiography rate a year and number performed a year were 1·65 per 1000 and 390. When adjusted for the different SMR, predicted rates per 1000 were 0·9, 1·5, 1·7, 2 3, 2·2, 3·2, and 3·3 for SDS 1–7 respectively. Observed rates were 1·7, 1·4, 2·2, 2·4, 2·3, 3·0, and 2·7 for SDS 1–7 respectively (excess 24, deficit 18 angiograms a year (200% and 83% of predicted) for SDS 1 *v* 7).

These data show a relative excess of referral for coronary angiography, particularly in women, in patients from areas of low social deprivation. This was not apparent from crude angiography rates. If, as seems likely, these rates approach the ideal then this suggests a significant need is not being met in patients from areas of high social deprivation.

Admission to hospital with suspected myocardial infarction, 1973–89: from the Nottingham heart attack register

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The Nottingham heart attack register was established in 1973 to monitor admissions to the Nottingham hospitals for suspected myocardial infarction. Analysis of over 20 000 admissions and the cases of over 8000 people who were declared dead on arrival was undertaken to identify trends in patient behaviour, involvement of the general practitioner and ambulance service before admission, management in hospital, and outcome. There was a fivefold increase in admissions, exceeding 4000 per year in 1989. The median delay from symptom onset to arrival in hospital decreased from over four hours to under three. A general practitioner was called to over 60% of those admitted. Nottingham ambulances conveyed an increasing proportion of an ever increasing number of patients, reaching 85% of all admissions by 1989; the number of 999 calls almost doubled. The number of men admitted always exceeded the number of women admitted, and men (particularly younger men) were always more likely to be admitted to a coronary care unit (CCU); by 1989 these differences were slight. Three quarters of patients with a confirmed myocardial infarction were treated initially in a CCU. Acute myocardial infarction was diagnosed on discharge in a quarter of admissions, a third having a possible myocardial infarction. Mortality declined generally from 18% to 10%, but men always fared better than women and those under 65 better than those over 65. CCU mortality fell from 18% to 10%, ward mortality fell from 27% to 10%, and myocardial infarction mortality was constant at 20%. Drug prescribing changed markedly. In 1973, 30% of patients received either digoxin or an antiarrhythmic drug, but only 10% by 1989; diuretic use was constant at about 45% and β blockers and anticoagulants were prescribed more frequently, in over a quarter by 1989. Temporary pacing, inotropic drugs, and intravenous vasodilator drugs were used infrequently.

Acute myocardial infarction shows no evidence of decline in Nottingham and demand for admission with suspected myocardial infarction continues to increase.

Blood selenium state of controls and patients with ischaemic heart disease and of healthy volunteers in Ayrshire and a survey of dietary selenium

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There is evidence that the atherogenic process is initiated by the free radical lipid peroxidation of low density lipoprotein and that this process can be inhibited by antioxidants—for example, vitamins A, C, and E. A strong inverse relation has been shown between mortality from ischaemic heart disease and plasma vitamin E concentrations (WHO/MONICA). Selenium, through its presence in the structure of the antioxidant enzyme glutathione peroxidase, is also involved in the damage limitation process by degrading potentially toxic lipid hydroperoxides. This paper reports the blood selenium state of 354 patients with ischaemic heart disease and matched controls in 1985 and of 478 volunteers participating in the Ayrshire heart health campaign three years later. It also presents data on the change in dietary selenium over the period 1985–90. The mean whole blood glutathione peroxidase activity for the 354 patients in 1985 was 8·16 U/ml and was highly significantly ($p < 0·001$) lower in patients with ischaemic heart disease (6 54 (0·41)) than in controls (9·57 (0·43)). In 1988 the mean activity was 6·08 (0·065) U/ml and was inversely correlated with white bread consumption and directly with wholemeal bread but not with oily fish consumption. Significant relations were also found with social class, age, and place of residence but not with a history of angina or previous heart attack. The numbers in these latter categories were low, however. Dietary selenium has declined from 43 μg/day in 1985 to around 30 μg/day in 1990 because of decreased use of imported Canadian wheat flour in bread making. The proportion of dietary selenium provided by cereals has fallen from 47% to 24%. The lower mean glutathione peroxidase activity recorded in 1988 is consistent with the decrease in dietary selenium since the previous survey in 1985. The two populations, however, may not have been entirely comparable.

Analysis of heart disease mortality data: inference on causality and prospects for primary prevention

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An important consideration in support of causality of association in epidemiological studies is specificity of the association between the putative "risk marker" and the disease under study. Nevertheless, many studies, both observational and experimental, investigate mortality from a single disease without comparison with a control disease or with "all causes." Reappraisal of methods of analysing mortality data and of presenting the results of analysis as (age standardised) proportions of all cause mortality creates case-control comparisons and helps to distinguish between more deaths and younger deaths, thereby overcoming an important limitation of the familiar standardised mortality ratio (SMR). Results of these analyses show that cigarette smoking, an important risk marker for heart disease, is not associated with more deaths from heart disease but rather with younger death from a number of causes (including heart disease). The lifetime risk of heart disease death is inversely associated with smoking: never 35%, light 34%, medium 32%, heavy 29%.

On present evidence and for the foreseeable future heart disease is not preventable: the later stages (severe disabling disease) and the final manifestation (death) may be postponable, which is not the same thing. These findings have implications both for preventive medicine and for health care planning.

Epidemiology of heart valve surgery in Ireland, 1956–85: a 30 year perspective

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Because of its small size Ireland affords a unique opportunity for population based research. From the mid-1960s to 1985 virtually all adult heart valve surgery was performed in one centre. The operative records for this centre and all the other available operative records for the country were reviewed. Data were entered on precoded data sheets, stored on an Amdahl 5860 mainframe computer, and analysed with the statistics analysis system (SAS) package. With triennial national census data, procedure rates per 100 000 of the population were calculated. The total number of operations increased from 27 in 1956 to 201 in 1979 and thereafter levelled off at a mean of 196 operations a year. The five year procedure rate per 100 000 population was 6·9 in 1956–60 and increased to 28·9 in 1980–5. The procedure rate for mitral valvotomies peaked at 18 5 in 1961–5 and fell to 2·5 in 1981–5. The mitral valve replacement rate increased from 0·2 in 1961–5 to a peak of 9·7 in 1976–80 and fell to 8·8 in 1981–5. The aortic valve replacement rate increased during each successive five year period, from 0·1 in 1961–5 to 17·6 in 1981–5. The double valve replacement rate remained approximately 3 0 for the three five year periods from 1971 to 1985. The aetiology of the disease in patients undergoing valve surgery changed dramatically; 68% had rheumatic valve disease in 1976 *v* 30% in 1985 and 10% had degenerative disease in 1976 *v* 40% in 1985. A progressive increase in mean age was observed also.

This review provides a unique national perspective on the trends in valve surgery over 30 years and affords an opportunity for rational health planning for the future.

Failure of provision of antibiotic prophylaxis for at risk cardiac patients

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Patients at risk of infective endocarditis may not be aware of the need for antibiotic prophylaxis and not receive appropriate advice or treatment. Questionnaires were sent to general practitioners and dentists and 189 at risk patients (aged 12–92 years, mean 62). Only 46% of patients recalled any advice about prophylaxis and 26% recalled written advice. Thirty per cent remembered receiving repeated advice. Only 21% could accurately recall specific instructions for prophylaxis. Half the patients attended a dentist, but only 12% had done so within one year and 39% and not attended in five years. Half told their dentist about their heart condition, 40% of these brought a doctor's note, and only 44% of all patients recalled receiving antibiotics before treatment. General practitioners' replies (262/480; 55% in 200 practices) indicated that 97% gave antibiotic advice but only 3% in writing. Only 50% took a dental history. Dentists' replies (72/240; 30% in 120 practices) indicated that 94% identified at risk patients on their register. Only 14% of general practitioners identified such cases, but 75% could adapt their register to do so. Most dentists (96%) and 57% of general practitioners would prescribe antibiotics recommended by the British Society for Antimicrobial Chemotherapy. Only half of the general practitioners and dentists thought that they received adequate advice from their cardiac centre. Up to half of the general practitioners and dentists did not know all of the cardiac conditions requiring prophylaxis.

This study shows important failures in dental care and provision of antibiotic prophylaxis for at risk patients. Improved communications are needed to address these problems.

Early experience with directional coronary atherectomy

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We assessed the safety and efficacy of the Simpson atherectomy catheter in 11 patients with eccentric lesions in a major coronary artery. Atherectomy was attempted in seven left anterior descending (LAD) vessels (seven lesions), one LAD graft, and three right coronary (RCA) vessels (four lesions). Two patients had angioplasty of other lesions. All patients were fully heparinised during the procedure and for 24 hours afterwards. A guiding catheter of 9 5 (RCA) or 11 (LAD) French gauge was introduced into the target vessel and the lesion was crossed with a 0·014 inch high torque floppy wire. The primary success rate (stenosis reduced to <50%) was 10/12 (83%). However, three of these vessels (all LAD) became occluded after 10 minutes (reopened by angioplasty), 24 hours (reopened by angioplasty with small enzyme activity increase), and 5 days (patient received internal mammary graft six weeks later) with no long term sequelae for the patients, who are now symptom free. The remaining six patients were followed up for a total of 25 months. Five remain well while one returned after six months with symptomatic restenosis at the atherectomy site, which was successfully treated by angioplasty. An average of 7·8 (range 4–12) cuts produced 3·8 (range 1–8) tissue pieces per patient. The number of tissue pieces and residual stenosis was not related (r = +0·3), suggesting that the mechanical displacement of atheroma (Dotter effect) is important in obtaining a good result. Individual histological features were present with varying frequency: fibrous tissue (100%), smooth muscle proliferation (50%), haemosiderin (30%), calcification (20%), cholesterol (20%), thrombus (20%), internal elastic lamina and part of media (10%). Two patients suffered complications, one left main stem dissection requiring non-emergency bypass grafting and one femoral artery occlusion.

The Simpson atherectomy catheter is a safe and practical form of treatment for discrete (<10 mm long) eccentric coronary artery lesions.

Excimer laser coronary angioplasty: initial experience in the United Kingdom

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Since February 1990 the 200+ dymer (Advanced Interventional Systems) excimer laser has been used to treat 58 patients in 63 procedures (52 in men, 11 in women; mean age 55·4 years, range 32–78). Thirty procedures (48%) were high risk (one or more of (*a*) left ventricular ejection fraction (LVEF) < 35%; (*b*) triple vessel coronary artery disease; (*c*) unstable angina; (*d*) need to treat a stenosis in the sole remaining coronary conduit). Nineteen procedures (31%) were in patients with present or recent unstable angina, 23 (37%) in patients turned down for (further) coronary surgery. LVEF averaged 55% (range 27% to 78%). There was a high incidence of previous myocardial infarction (43%), previous bypass graft surgery (CABG) (37%), previous balloon angioplasty (PTCA) (32%). Fifteen laser treated lesions in 11 patients were restenoses after PTCA and seven lesions in five patients required repeat excimer laser coronary angioplasty (ELCA) or PTCA, or both, for restenosis after ELCA. Of the 112 lesions available for treatment, 29% were short (<5 mm long), 49% were intermediate (5–15 mm long), and 22% long (>15 mm long). Fifty seven lesions were treated by ELCA alone (reducing mean per cent stenosis from 74 (SD 13·2) to 24 (10·5)), 37 by ELCA and PTCA (stenosis reduced from 82 (12·4) to 23 (20·7)), and 16 by PTCA alone (stenosis reduced from 72 (11·5) to 15·3 (13·4)). In this high risk group of patients there were three procedure related deaths (one ELCA related, 10 hours after the procedure, and two PTCA related, one 72 hours after the procedure and the other during the procedure); one late death 10 weeks after the procedure; two acute thrombotic closures due to inadequate early heparin dose; three extensive and six minor dissections; one perforation; five spasm; two late small coronary artery aneurysms; two myocardial infarction (one ELCA and one PTCA related); two distal coronary emboli. No patient required emergency coronary artery bypass grafting.

Long term follow up of self expanding stents

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Coronary artery stents were developed to treat abrupt vessel closure during coronary angioplasty (PTCA) and to control restenosis. Between 1986 and 1989, 132 patients underwent stent implantation with 171 self expanding mesh stents. Stent implantation into native coronary vessels was undertaken as a primary procedure to treat acute myocardial ischaemia in 29 patients (after PTCA in 24 and unstable angina in five) with 34 stents. Elective stent insertion for native vessel restenosis was performed with 71 stents in 61 patients, and 66 stents were deployed electively in saphenous vein coronary bypass graft (CABG) stenosis in 42 patients. The postimplantation course during a follow up period of 1 to 34 (mean 17) months was uncomplicated in 101 (76·5%) patients. Thrombotic stent occlusion before discharge occurred in eight (6·1%) patients and was treated conservatively in two, by PTCA in four, and by CABG in three (after unsuccessful PTCA in one case). Surgical repair of the femoral artery was required in eight patients (6·1%) because of persistent bleeding in the presence of anticoagulant treatment. Among the group who underwent urgent stent implantation, restenosis requiring repeat PTCA occurred in one (4%) patient and an additional four patients (13%) required further intervention (PTCA or GABG) for other disease. After elective stent implantation into native vessels symptomatic restenosis occurred in four (6·6%) patients and intervention for different disease was required in a further four (6·6%). After stent implantation into coronary artery bypass grafts restenosis occurred in three (7%) and an additional six (14·3%) patients underwent repeat intervention for different lesions. There were nine deaths (mortality 6·8%) during follow up, three in each group. Management of anticoagulation after stent implantation may be difficult but the PTCA restenosis rate is reduced considerably, and this may be the procedure of choice for the management of CABG stenosis.

Combined coronary angioplasty and ultrasound imaging catheter: initial in vivo studies in humans

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Intravascular ultrasound allows direct visualisation and characterisation of the arterial wall and measurement of luminal cross sectional area and wall thickness. This has particular potential for coronary angioplasty procedures. We have tested a new combined coronary angioplasty and ultrasound imaging catheter (Endosonics) which allows immediate assessment of the vessel wall during and after balloon angioplasty. It consists of a 2·5 or 3·0 mm percutaneous transluminal coronary angioplasty balloon with an integral synthetic aperture transducer. The balloon profile is 0·044 inch and the transducer profile 0·072 inch. It uses a standard 0·014 inch guide wire. This combined catheter was used to perform coronary angioplasty in 10 patients. Trackability and movement over the wire within the coronary vessels was good. Pushability against the lesions was similar to that of a standard balloon catheter. In one patient we were unable to cross the lesion because of the high balloon profile. Satisfactory images were obtained in eight patients providing information on the vessel wall and luminal diameter. Ultrasound imaging influenced our management in two out of the eight cases. In one a significant stenosis was present that was not convincingly shown on angiography. In another there was a significant residual stenosis on ultrasonography requiring redilatation with a larger balloon resulting in definite improvement on ultrasound despite what appeared to be a good initial angiographic result. In two patients no images were obtained, in one for unknown reasons and in one because persistent manipulation of the catheter in attempting to cross the lesion led to loss of the signal.

We conclude that this combined catheter assists in the performance of percutaneous transluminal coronary angioplasty and may allow characterisation of the vessel wall not achievable with standard angiography. In some cases, however, image quality was hampered by the presence of air bubbles trapped in the balloon. Future technical developments should include lower balloon and transducer profiles and improved balloon venting mechanisms to allow optimal image quality.

Can ω 3 fatty acids reduce percutaneous transluminal coronary angioplasty restenosis rate?

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Restenosis of a coronary artery dilated by coronary angioplasty (PTCA) occurs in up to 40% of lesions. We investigated whether ω 3 fatty acids (Maxepa) administered 1–2 days before and for six months after angioplasty could reduce this restenosis rate. A total of 120 consecutive patients who underwent PTCA to one or more stenoses were randomly assigned to standard treatment plus 1·8 g eicosapentaenoic and 1·2 g docosahexaenoic acid daily (group A, $n = 60$) or to standard treatment alone (group B, $n = 60$). There was no statistical difference between groups in baseline characteristics. Quantitative angiography at a mean 31·4 weeks after angioplasty occurred in all patients in group A but in only 53 in group B. Primary angiographic success was defined as a lesion of $>50\%$ diameter stenosis reduced to half of the initial diameter stenosis and restenosis as a loss of $>50\%$ of initial angiographic improvement in those lesions with a primary success. In group A 106 lesions were dilated, with angiographic success in 79. Restenosis occurred in 27·8% of these. In group B 96 lesions were dilated, but only 87 had angiographic follow up. Angiographic success occurred in 60, of which 28·3% restenosed (NS; group A *v* B). There was no significant difference between group A and group B in the mean diameter stenosis before and immediately after angioplasty or at follow up angiography. Twenty seven patients required a further revascularisation procedure in the year after angioplasty (22 *v* 15, A *v* B; NS). Return of anginal symptoms during the six months after angioplasty occurred in 51·7% of group A and 55% of group B (NS).

In conclusion, administration of capsules containing ω 3 fatty acids in the quantity used 1–2 days before angioplasty and continued for six months conferred no benefit in restenosis rate, recurrence of symptoms, or need for a further revascularisation procedure.

Restenosis after coronary angioplasty: role of preangioplasty stenosis morphology

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To assess the role of precoronary angioplasty (PTCA) stenosis morphology on restenosis, 41 patients (47 stenoses) who underwent repeat angiography $\geqslant 3$ months (mean 11 (1·5)) after PTCA were studied. Coronary stenosis diameter, area, symmetry, and morphology were assessed by computed quantitative coronary angiography before and immediately after PTCA and on follow up angiography. Before PTCA 18 stenoses were concentric (symmetric narrowings with smooth borders), 12 eccentric (asymmetric narrowings with smooth borders), and 17 irregular (three or more serial severe, closely spaced obstructions in a coronary artery) or type II eccentric (asymmetric narrowings with scalloped or multiple irregular borders). Restenosis occurred in 18 lesions: two (11%) concentric, four (33%) eccentric and 12 (70%) irregular or type II ($p < 0{\cdot}05$), while 29 lesions remained unchanged. Stenosis diameter, area, and symmetry before and immediately after PTCA were similar in the 18 patients with and the 23 patients without restenosis. The follow up angiogram showed that 11 (61%) stenoses in the restenosis group and 18 (63%) in the no-restenosis group had similar morphology to that before PTCA. Restenosis occurred in seven (30%) patients with chronic stable angina and in 11 (61%) with unstable angina ($p < 0{\cdot}05$). In patients with stable angina one (8%) concentric stenosis, two (25%) eccentric stenoses, and four (80%) irregular lesions restenosed. In patients with unstable angina one (25%) concentric, two (50%) eccentric, and eight (66%) irregular lesions restenosed.

Stenoses that were irregular before PTCA tended to adopt an irregular morphology if they recurred, whereas concentric stenoses rarely recurred. These findings indicate that irregular and type II eccentric stenoses are associated with a higher risk of restenosis than are concentric stenoses. In most cases the morphology of a restenosed lesion is similar to that observed before PTCA.

Cardiac manifestations of Marfan's syndrome: improved evaluation with transoesophageal echocardiography

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Aortic root pathology is common in Marfan's syndrome but is not well visualised by conventional transthoracic echocardiography. Transoesophageal echocardiography (TOE) can provide high resolution imaging of the heart and great vessels and may be valuable for the diagnosis of aortic dissection in such patients. We performed TOE in 14 patients (aged 19–56 years) known to have Marfan's syndrome. Eight patients had suspected aortic dissection, four had inadequate results from transthoracic studies, and two patients had endocarditis postoperatively, one after aortic root and valve replacement and one after mechanical mitral valve replacement for myxomatous valve degeneration. Excellent visualisation was obtained in all patients with TOE. Aortic dissection was shown in seven patients (type I dissection in six, chronic type III dissection in one). In all seven patients the extent of the dissection, entry and exit points, true and false lumen, and the presence of aortic regurgitation or pericardial effusion, or both, were identified in addition to diagnostic confirmation. The TOE findings of aortic dissection were confirmed at surgery in five patients, at necropsy in one patient, and on computed tomography in the patient with type III dissection. In the four patients with inadequate results from transthoracic echocardiographic studies TOE allowed assessment of aortic root dimensions, the presence of mitral valve prolapse, and aortic regurgitation. The patient with endocarditis after root replacement had an aortic root fistula shown on TOE, with flow identified between the layers of the Dacron wrap and the native aortic root. The remaining patient with suspected endocarditis on a mechanical mitral valve replacement had vegetations shown at TOE which had not been seen on transthoracic imaging. In both patients the TOE findings were confirmed at the time of surgery.

TOE can provide important and rapid diagnostic information in patients with Marfan's syndrome and has altered the approach to diagnosis and follow up in such patients.

Biplane transoesophageal echocardiography: valuable new diagnostic information or simply more of the same?

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With the introduction of a second ultrasound array scanning in the longitudinal plane, the morphological and functional information which may be obtained during a transoesophageal (TOE) study is potentially increased. To determine what, if any, new diagnostic insights might be obtained by this addition, we carried out a prospective study to compare and contrast the findings obtained by an initial transverse plane study with (*a*) information from a subsequent longitudinal plane study alone and (*b*) information derived by integrating both imaging planes. All patients had confirmation of the biplane TOE findings at either catheterisation or surgical inspection, or both. Sixty one patients were included in the study (age range 9–78 years). Referral diagnoses included suspected mitral prosthetic dysfunction (17), mitral stenosis (four), mitral regurgitation (all being considered for valve repair) (seven), acute infarct complications (four), atrial septal defects (nine), complex congenital heart disease (11), aortic coarctation (three), aortic dissection (three), and suspected endocarditis (three). When the information derived from each plane was compared with the definitive diagnosis (integrated biplane TOE and correlative catheterisation or operative findings, or both) complete diagnostic information was derived from the transverse plane alone in only 78% of patients and from the longitudinal plane alone in only 65%. Clinically important new (21%) or additional (36%) morphological information was obtained from long axis scanning in 37/61 patients. Morphology better studied by long axis scanning included native mitral and tricuspid valve leaflet and subvalve morphology (17/28); anterior and posterior sites of mitral paravalvar leakage (8/17); lesions of the apex, posterior, and anterior walls of the left ventricle (3/3); defects in the anteroinferior atrial septum (4/9); the right ventricular outflow (61/61); proximal left pulmonary artery (40/61); and ascending aorta (1/3). The maximal diagnostic value biplane TOE was obtained only when morphological and haemodynamic information obtained from both imaging planes was integrated. This gave a diagnostic accuracy of 98% for biplane TOE *v* 86% for cardiac catheterisation in the 39 patients who had subsequent detailed surgical description.

Transoesophageal echocardiography in patients with focal cerebral ischaemic events: glamorous toy or clinically useful tool?

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The detection rate of cardiac sources of emboli (SOE) with precordial echocardiography (PE) in patients with focal ischaemic cerebral events is low. To investigate the role of transoesophageal echocardiography (TOE) 131 consecutive patients with such events were studied with both PE and TOE contrast studies. TOE detected 18 potential right to left (R-to-L) shunts and two cases of valve vegetations not detected by PE, and spontaneous contrast echos (SCEs) were found in 27 out of 28 patients with a large left atrium—three with left atrial thrombus. A clinical cardiac abnormality had been found in 53 patients; mitral valve prolapse (MVP) was confirmed in four; 25 patients with chronic atrial arrhythmias had a large left atrium (24 with SCEs, three with left atrial thrombus); valve disease was confirmed in 14; and 10 had potential R-to-L shunts. Seventy eight patients had no clinical cardiac abnormality: six had MVP, 17 had potential R-to-L shunts, and one had a left ventricular regional wall motion abnormality. TOE is thus more sensitive than PE for the detection of potential SOE in these patients. However, except for the detection of a R-to-L shunt, the yield in patients with no clinical cardiac abnormality is low. Moreover, the abnormalities detected in those with overt cardiac disease merely confirm the clinical diagnosis. Patients with left atrial spontaneous contrast echos may benefit from anticoagulation but this requires further study. Until more data are available on this feature and the role of R-to-L shunts in this population, the role of echocardiography (precordial or transoesophageal) remains limited.

Transoesophageal versus transthoracic echocardiography in assessment of systemic and pulmonary venous connections

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To determine the diagnostic accuracy of transoesophageal echocardiographic (TOE) and transthoracic (TTE) studies in the definition of either systemic or pulmonary venous connections, 86 unoperated children (aged 0·2–14·8 years, mean 3·8 years) with congenital heart disease were prospectively studied by both techniques. The results obtained were correlated with one another, subsequent surgical inspection (n = 53), which served as the gold standard, and cardiac catheterisation (n = 78). Normal systemic and pulmonary venous connections were defined by TOE in 72 of the 86 patients and all were confirmed by surgical inspection or cardiac catheterisation, or both. Systemic venous connections could be defined by TOE in all. The drainage of all four pulmonary veins could be documented by TOE in 92% of all children studied. Nineteen anomalous venous connections were documented by TOE in 14 patients. These were confirmed in all but one child who awaits surgical correction. In contrast, TOE allowed the definition of only eight of these 19 anomalous venous connections (42%). Partial anomalous pulmonary venous connections were documented by TOE in six out of six patients, by TTE in only two out of six. In one patient in whom TTE suggested total anomalous pulmonary venous drainage the TOE study defined a mixed pattern of drainage, which was confirmed at surgery. Anomalies of the superior caval venous system were documented by TOE in nine patients, whereas these were identified in only three by TTE. Anomalies of the inferior caval vein (three patients) were equally well identified by either technique. When compared with angiocardiography TEE provided additional valuable morphological information on the venous connections relative to the atrial septum in complex congenital heart disease. None of the patients in whom TOE showed normal venous connections was found either by surgical inspection or cardiac catheterisation to have anomalous venous connections.

TOE is a highly sensitive and most versatile tool in the preoperative definition of systemic and pulmonary venous connections. In this series it was largely superior to TTE and of additional value to cardiac catheterisation and angiocardiography.

Can intravascular ultrasonography affect the outcome of vascular procedures?

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Recent interventional techniques demand greater operational feedback, beyond the limits of conventional imaging systems. We assessed intravascular ultrasonography (IVUS) in five coronary and 18 peripheral arteries (23 patients) during varying combinations of laser and balloon angioplasty (PTCA, n = 21), atherectomy (n = 6), and endovascular stent implants (n = 8). IVUS was performed with a rotating 20 MHz probe. This was compared with angiography (all cases) and angioscopy (five cases). Diseased *v* normal arteries and stents were well defined with IVUS in 21 out of 23 patients (two failures: one mechanical, one poor access). Wall morphology, plaque mapping (eccentric *v* concentric), and tissue characterisation was possible in all 21 cases. On line measurements allowed luminal cross sectional area, diameter, and percentage stenosis calculations in 20 cases. The immediate effect of vascular manipulations was evident in all. Successful PTCA was associated with significant wall disruption (plaque rupture, splitting of intima or media) in 12 out of 15 cases. In atherectomies IVUS was very useful in showing the extent of debulking, wall thinning, residual disease, and the relative lack of wall disruption compared with PTCA. Likewise, IVUS showed stent deployment and expansion in eight out of eight cases *v* six out of eight with angiography. Online data were valuable in selecting the most appropriate mode of treatment and the balloon or stent size and in assessing the therapeutic outcome, complications, and extent of residual disease not apparent on angiography or angioscopy.

IVUS itself materially affected the outcome of atherectomies and stent procedures. Although IVUS contributed usefully to PTCA, it did not significantly alter the final outcome (success *v* failure) additional to angiography.

Morphological assessment of pulmonary vascular disease by intra-arterial ultrasonography

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Intra-arterial ultrasonography allows direct and accurate visualisation of vessel wall morphology. To evaluate its potential role in pulmonary vascular disease we studied eight patients (age range 7–59 years) undergoing routine, diagnostic right and left heart catheterisation. Cardiac pathologies were dilated cardiomyopathy (two patients), ventricular septal defect (two), atrial septal defect (one), primary pulmonary hypertension (one), multiple pulmonary emboli (one), and mitral stenosis (one). Real time, cross sectional images of the pulmonary artery (PA) and its branches were obtained with a 20 MHz ultrasound transducer rotating in a 100 cm long, 2 mm in diameter sterile sheath which was advanced into the pulmonary artery under fluoroscopic guidance. Seven out of eight studies were successfully completed; in one patient the right heart was very dilated and adequate positioning of the transducer was not possible. Normal arterial, cross sectional morphology was seen in three patients, two with normal PA pressures and one whose mean PA pressure was 60% of mean systemic arterial pressure because of atrial septal defect. In three patients with systemic level PA pressures owing to ventricular septal defect (two) and primary pulmonary hypertension (one) thickening of the intimal and medial layers and areas of intimal proliferation were seen. In the patient with multiple pulmonary emboli, intravascular, mural thrombus was detected at several sites.

Intra-arterial ultrasonography can differentiate normal from abnormal pulmonary arterial wall morphology in patients with and without pulmonary hypertension. It may thus become an important investigation in the diagnosis and assessment of pulmonary vascular disease.

Regression of cardiac hypertrophy achieved by high dose propranolol treatment in children and adults with hypertrophic cardiomyopathy

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High dose oral propranolol treatment (7–18 mg/kg/day) is being used to treat a series of patients with hypertrophic cardiomyopathy. The group now comprises eight infants who presented with congestive heart failure and failure to thrive or syncope, or both; four children with progressive worsening of hypertrophic cardiomyopathy or severe ventricular arrhythmias, or both; and three adults with angina and near syncope or severe ventricular arrhythmias, or both. The group has been treated for a total of 68 patient years with no deaths; all patients are symptom free except the most recently recruited adult. Two infants presenting with severe symptomatic hypertrophic cardiomyopathy have remianed well over a 10 year follow up. All 15 patients have shown electrocardiographic and echocardiographic evidence of regression of pathological cardiac hypertrophy. Because 12 of the patients are still growing echocardiographic measurements have included not only absolute measurements of wall thickness and cavity dimensions but also calculation of diastolic and systolic ratios of wall thickness to cavity diameter. The observations were compared to pretreatment values in the same patient. In 12 patients treated for at least one year the Wilcoxon signed rank test showed that high dose propranolol produced a significant reduction in absolute septal thickness (-24%; $p < 0·01$); diastolic septum to cavity ratio (-38%); $p < 0·0025$); posterior left ventricular wall hypertrophy, when present (-44%; $p < 0·013$); systolic left ventricular wall to cavity ratio (-37%; $p < 0·01$); and a reduction in ejection fraction towards the normal range (-11%; $p < 0·013$). The serum propranolol concentrations required to produce regression of hypertrophy were 150–1360 μg/l ("normal" therapeutic range 50–100 μg/l). Five patients needed the addition of disopyramide to control their arrhythmias.

It is concluded that high dose propranolol abolishes symptoms and greatly improves survival in infants with symptomatic hypertrophic cardiomyopathy and that this treatment can induce regression of hypertrophy in both children and adults with this condition if care is taken to achieve a profound 24 hour β adrenoceptor blockade.

Endothelin may be a circulating vasoconstrictor in chronic heart failure

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Endothelins (ET) are potent long acting vasoconstrictor peptides. As chronic heart failure is characterised by reduced peripheral and renal perfusion we measured ET concentrations in patients with this syndrome with a previously described assay. Ten healthy controls aged 52 (3) years (three women) were compared with 12 patients aged 64 (5) years (all men) with chronic heart failure (three New York Heart Association class IV, eight class III, one class II) treated with diuretics, digoxin, and vasodilators. The mean plasma ET concentration in controls was 5·9 (SEM 0·2) pmol/l compared with 13·6 (1·0) pmol/l in patients ($p < 0·01$). Eight patients exercised on a treadmill. Plasma ET concentrations did not increase further with maximum exercise (11·4 (1·6) before exercise *v* 10·5 (1·6) afterwards). In a second study 13 patients aged 29–70 years (four men) with chronic heart failure were investigated at the time of cardiac catheterisation. Significant renal extraction of ET was found: the concentration of ET in the aorta was 11·1 (0·8) pmol/l and in the renal vein 8·8 (0·6) pmol/l ($p = 0·02$). Thus ET concentrations are raised in chronic heart failure either from increased secretion or from decreased clearance. Increased secretion may occur to maintain arterial pressure in the face of a limited cardiac reserve; however, the cardiovascular stress of upright exercise did not further increase plasma concentrations. Reduced clearance, due to poor renal perfusion, could also account for the raised plasma ET concentration in heart failure as these results show, for the first time, that ET is extracted by the kidneys.

Vasoconstriction is pathophysiologically important in heart failure and raised ET concentrations may contribute to this.

Improved lymphocyte β receptor function and cardiac pumping capacity after converting enzyme inhibition in heart failure

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Cardiac β receptor down regulation in heart failure causes reduced sensitivity to β agonists. We have previously showed that lymphocyte β receptor (LBR) down regulation in heart failure can be partially reversed by captopril. We studied 12 patients with severe heart failure (New York Heart Association class III/IV) before and after 16 weeks of oral quinapril treatment to determine whether LBR up regulation in response to an angiotensin converting enzyme inhibitor is associated with a concomitant improvement in cardiac β receptor function. This was assessed by measuring invasive haemodynamic variables during bicycle exercise and incremental β agonist (dobutamine) infusion. After quinapril LBR function (in vitro isoprenaline stimulated lymphocyte cAMP production) improved significantly: at 15 mmol/l the cAMP concentration was 376% of control values after quinapril *v* 211% before quinapril, $p < 0·02$. There were associated increases in cardiac index (3·8 to 4·4 l/min/m^2, $p < 0·01$), stroke volume (63 to 75 ml, $p < 0·05$), and cardiac power output (1·7 to 2·0 W, $p < 0·05$) at peak exercise. Similarly, with dobutamine at 10 μg/kg/min cardiac index increased from 4·0 to 4·6 l/min/m^2 ($p < 0·05$), stroke volume from 70 to 82 ml ($p < 0·01$), stroke work index from 0·42 to 0·50 J/m^2 ($p < 0·05$), and cardiac power output from 1·5 to 1·8 W ($p < 0·05$).

We conclude that LBR up regulation seen in patients with severe heart failure in response to angiotensin converting enzyme inhibitors is associated with an improved cardiac response to exercise and dobutamine consistent with functional myocardial β receptor upregulation.

Dilated cardiomyopathy: high incidence of antimyolemmal antibody mediated cytolytic activity in cases of recent onset

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Circulating antimyolemmal antibodies (AMLA) have been detected in about 30% of patients with chronic dilated cardiomyopathy but their incidence in acute cases is unclear. Over 24 months seven consecutive patients with dilated cardiomyopathy (age 44 (14)) and symptoms for less than six months were studied. All had a full virology and autoantibody screen, cardiac biopsy, and cross sectional echocardiography; fractional shortening for the group was 12% (4%). The presence of circulating AMLA was assessed in vitro with intact rat and human cardiocytes and the indirect immunofluorescence test. Serum cytolytic index for AMLA (half life of cardiocytes in patients serum − half life in control serum) was measured in a microcytotoxicity assay with living rat cardiocytes as target cells. Data were compared with that in 70 controls evaluated in the same laboratory (normal range 0 92 (0·07), effective cytolysis $<0{\cdot}75$). Only one patient had positive viral serology, which was for recent coxsackie B2 infection. Autoantibody screening was negative in all. Light microscopy of biopsy samples showed non-specific appearances in two patients; focal myocarditis was found in one case and healing or healed myocarditis in four cases. The cytolytic index for the group was 0·51 (0·05) (range 0·47–0·6, $p < 0{\cdot}05$). Significant binding of IgG, IgM, or polyvalent antibodies to AMLA bound to rat or human cardiocytes was present in all seven; five patients were positive with all three markers, and four of these had strongly positive binding on at least one test.

Circulating AMLA are commonly present in dilated cardiomyopathy of recent onset. Their detection might reflect ongoing disease activity, give insight into the immunopathogenesis, and may help identify patients likely to benefit from immunosuppressive treatment.

Cardiac abnormalities associated with HIV infection

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To determine the prevalence of cardiac abnormalities for the first time in a United Kingdom based population infected with HIV 74 patients (53 male, 21 female) infected with HIV for between 32 and 87 months were recruited as part of a prospective echocardiographic study. They comprised the two major risk groups for HIV infection: intravenous drug abusers (57 patients, 36 male, 21 female; mean age 28·9 years; mean CD4 count 205 cells/mm^3 (normal range 500–1500 cells/mm^3)) and homosexuals (17 patients; mean age 34·2 years; mean CD4 count 38 cells/mm^3). Ventricular size and function were estimated by standard cross sectional and M mode echocardiographic techniques. Detailed analysis was undertaken by two independent observers. Seven (9·5%) patients (five homosexuals, two intravenous drug abusers) had global left ventricular dysfunction. Their mean CD4 count was 32 cells/mm^3, indicating end stage disease. There was an excess of homosexuals in this group (29% affected *v* 4% of intravenous drug abusers), possibly a reflection of their more advanced HIV disease. Left ventricular dilatation (end diastolic diameter >58 mm) without evidence of dysfunction was found in a further five (6·8%) patients (mean CD4 count 227 cells/mm^3), all intravenous drug abusers. These abnormalities were related neither to infection with toxoplasma (as judged by the toxoplasma dye test) nor to duration of treatment with the potentially cardiotoxic agent zidovudine (mean 16·3 months). Isolated right ventricular dilatation was found in seven (9·5%) patients (mean CD4 count 153 cells/mm^3) and occurred exclusively in intravenous drug abusers.

In conclusion, we found a high prevalence of dilated cardiomyopathy in HIV infection. This occurs in both major risk groups and seems to be a feature of end stage disease. It may be preceded by left ventricular dilatation. Isolated enlargement of the right ventricle may be a function of intravenous drug abuse rather than HIV infection.

Tumour necrosis factor may contribute to development of "cardiac cachexia"

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A significant proportion of patients with chronic heart failure suffer generalised wasting, which in its most extreme form is referred to as "cardiac cachexia." Inadequate nutritional intake is not thought to be the major aetiological factor. Instead it is suggested that a catabolic state is brought about through the actions of a circulating factor; a polypeptide with such actions has been identified and named tumour necrosis factor (TNF). We have measured plasma TNF concentrations in 26 consecutive patients admitted for investigation or treatment, or both, of chronic heart failure (due to coronary artery disease in 17, valve disease in seven, dilated cardiomyopathy in one, and congenital heart disease in one). The condition of all patients was New York Heart Association class III or IV and was treated with diuretics; most patients also received digoxin and an angiotensin converting enzyme inhibitor. Once treatment was optimised subcutaneous fat was measured (fat content rather than weight was measured to circumvent the potential problem of residual fluid retention). Using calipers a single observer measured bicep, tricep, infrascapular, and suprailiac skinfold thickness in quadruplicate (skinfolds over the lower part of the body were avoided because of the possibility of dependent residual fluid retention). Percentage body fat content was derived from the sum of the mean of each of these skinfold measurements by using standard tables. Patients were prospectively grouped as "cachectic" (male $<27\%$, females $<29\%$ body fat) or "not cachectic." TNF was measured in venous blood "blind" to group allocation with a sensitive radioimmunoassay. Sixteen patients (11 male) were cachectic (mean body fat content 21% (SD 4·8%)). Of these, nine had a raised (>15 pg/ml) concentration of TNF. Mean TNF in this group was 74 (SEM 20) pg/ml. Ten patients were not cachectic (body fat 31% (3·3%)); only one had a raised TNF concentration, which was 22 pg/ml (difference between groups, $p < 0{\cdot}001$). TNF was unmeasurable (<15 pg/ml) in plasma from five normal subjects.

TNF causes cachexia in experimental animals and catabolism in humans; it may also contribute to wasting in chronic heart failure. TNF has other actions, such as promoting clotting and inducing anaemia, which may also be undesirable in chronic heart failure.

Blood flow patterns at arterial bifurcations depend on vasomotor tone and heart rate

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Vasomotor regulation by endothelium derived relaxing factor depends on pulsatile blood flow patterns, which depend on arterial tone and heart rate. The effects of vasoactive drugs and pacing on flow were studied by 20 MHz Doppler velocimetry to measure velocity profiles and waveforms at exposed bifurcations in eight paced anaesthetised dogs. A calcium antagonist, YM-09730-5 (50 μg), increased the peak velocity (+25% (SD 9%), $p < 0{\cdot}05$) and duration (+48% (6%), $p < 0{\cdot}05$) of forward flow and reduced peak reverse flow velocity (−17% (5%), $p < 0{\cdot}05$). Conversely, angiotensin II (1 μg/min) reduced the peak velocity (−21% (5%), $p < 0{\cdot}05$) and duration (−23% (4%), $p < 0{\cdot}05$) of forward flow. Glyceryl trinitrate (150 μg/min) reduced peak forward velocity (−14% (4%), $p < 0{\cdot}05$) but prolonged both forward (+27% (6%), $p < 0{\cdot}05$) and reverse flow (39% (7%), $p < 0{\cdot}05$). Peak velocity and duration of forward and reverse flow were all greater when the dogs were paced at 1 Hz rather than 2 Hz (forward flow 52 (22) *v* 40 (16) cm/s and 131 (40) *v* 119 (28) ms; reverse flow −19 (8) *v* −15 (7) cm/s and 145 (30) *v* 115 (25) ms; $p < 0{\cdot}05$). Changes in velocity wave forms were accompanied by changes in velocity profiles.

Both vasoactive drugs and heart rate changes alter arterial bifurcation blood flow patterns in intact animals and may thus alter release of endothelium derived relaxing factor.

Energy wave generation by the left ventricle: influence of contractility and vasomotor tone

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Aortic flow is dominated by accelerating and decelerating waves generated by the left ventricle (LV), detectable as positive peaks of wave intensity, dP/dU (P, pressure and U, velocity) in early and late systole (compression and expansion waves respectively). As vasomotor tone and LV contraction influence aortic flow differently, we calculated aortic dP/dU in 13 anaesthetised closed chested dogs before and during pharmacological inotropic ($n = 6$) and vasomotor ($n = 7$) manipulation. Peak LV compression wave intensity, causing aortic acceleration, was increased by dobutamine 15 μg/kg/min (mean change +146% (SEM 17%), $p < 0{\cdot}01$) and decreased by propranolol 10 mg (−59% (5%), $p < 0{\cdot}01$). However, the compression wave was also dependent on vasomotor tone as its peak intensity was reduced by vasoconstriction with methoxamine 2 mg (−62% (6%), $p < 0{\cdot}01$). Peak LV expansion wave intensity, causing late systolic deceleration, was unaltered by inotropic manipulation or by vasoconstriction but was reduced by vasodilatation with glyceryl trinitrate 0·02 mg/kg/min (−25% (8%), $p < 0{\cdot}01$), due to the delayed arrival in the aorta of reflected waves with negative wave intensity.

Thus LV compression wave amplitude indicates LV contractile state but depends also on vasomotor tone, being decreased by vasoconstriction. Late systolic aortic flow deceleration depends more on vasomotor tone than the contractile state of the LV.

Rapid oxidation of plasma low density lipoprotein fraction in coronary artery disease

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Even under normal circumstances there are large fluxes of low density lipoproteins (LDL) through the intima. Evidence from animal experiments and from cell culture in vitro indicates that when LDL are modified by oxidation they are still taken up by macrophages but cannot be further processed; so that they become foam cells. Thus oxidised LDL may lead to atheroma, and the susceptibility of LDL to oxidation may be as important for atherogenesis as the absolute concentrations of LDL. We therefore determined whether plasma LDL is more readily oxidisable in patients with coronary artery disease. Venous blood samples were obtained from 10 patients aged 43–67 with coronary artery disease, and from 10 controls. The LDL fraction was separated by density gradient centrifugation (1·019–1·063) and dialysis. During incubation with copper ions the rates of (*a*) disappearance of carotene, (*b*) appearance of conjugated dienes, and (*c*) appearance of lipid peroxides were monitored spectrophotometrically. LDL oxidised more rapidly in patients with coronary artery disease than they did in controls ($p < 0{\cdot}02$).

Increased oxidisability of plasma LDL may contribute to atheroma in patients with coronary artery disease. Practical implications are (*a*) that drugs protecting LDL against oxidation may slow or prevent atherogenesis and (*b*) that measurements in young subjects might identify those at high risk of developing future coronary artery disease.

Direction of ventricular activation influences timing of repolarisation

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Ventricular arrhythmias are frequently initiated by an ectopic focus acting as a trigger. The reason why some ventricular ectopic beats or even short runs of ventricular tachycardia are benign is unclear. One possible mechanism may be the effect of an alteration in the direction of activation on the timing of repolarisation. To assess this possible mechanism we used the monophasic action potential (MAP) as a measure of repolarisation. The direction of activation was altered between one atrial and two ventricular sites. Atrioventricular (AV) sequential pacing was incorporated to minimise any possible effects of loss of atrial contribution to ventricular filling. Twelve patients (10 men; aged 50–66 years) were studied. Four catheter electrodes were positioned: (*a*) MAP on left ventricular lateral wall, (*b*) MAP on right ventricular septum, (*c*) pacing electrode in right ventricular apex, (*d*) pacing electrode in atrial appendage. Steady state atrial pacing was established and the pacing site sequentially switched in turn from atrium to ventricle to atrium to AV sequential to atrium. The positions of the right ventricular MAP catheter and right ventricular pacing electrode were interchanged and the sequence repeated. Peak systolic pressure changes (mean (SD)) during switching between the different pacing modes were as follows: atrial to ventricular 134 (SD 9) to 100

(5) mm Hg ($p < 0·001$) and atrial to AV sequential 152 (20) to 144 (16) mm Hg (NS). The MAP duration altered in all patients, with the altered pacing sequence either lengthening or shortening. The mean changes in MAP duration associated with alteration in pacing orientation between atrial to ventricular and atrial to AV sequential were similar, being 5·6 (5·1) ms and 6·3 (4·5) ms respectively (NS). The MAP changes were therefore primarily a function of altered direction of activation as opposed to pressure changes. In one patient with severe left ventricular dysfunction pacing from the apex of the right ventricle reproducibly induced prolongation of the left ventricular MAP by 40 ms with electrical alternans of 30 ms whereas pacing from the right ventricular septum failed to do so.

These preliminary results suggest that altering the site of ventricular activation alters the timing of repolarisation in the right and left ventricles. Although electrotonic interactions cannot be excluded, such findings accord with the hypothesis that changing the sequence of contraction of the ventricular fibres and thereby altering the stress or strain between neighbouring fibre groups may induce electrophysiological effects sufficient to generate clinically significant arrhythmias.

Mortality in outpatients awaiting coronary arteriography

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Facilities for coronary arteriography are limited in the United Kingdom, and correct selection of patients for this investigation is important to make best use of the resources available. It is equally important to consider the delays involved and to identify patients at high risk of cardiac events who require urgent investigation. At a cardiac centre with on site surgery the waiting list for coronary arteriography was audited over a four month period. During this time 934 cardiac catheterisation procedures were performed, including 592 coronary arteriograms for ischaemic heart disease (138 patients were transferred from other hospitals, 101 from home on the urgent waiting list, and 353 from home on the routine waiting list). Outpatients were assigned by a consultant cardiologist to the urgent waiting list (delay 0–3 weeks, mean 1 week) or to the routine waiting list (delay 3–12 weeks, mean 4·5 weeks). During the four month period seven patients died at home while awaiting admission for arteriography. One patient died two weeks after entry on to the urgent list, corresponding to 0·9% of admissions from the urgent list over the four months. Six patients died 3–9 (mean 6) weeks after entry on to the routine list, corresponding to 1·7% of routine admissions. Patients who died were aged 45–67 with angina grades II–IV; two were diabetic and one had mild heart failure. The mode of death ascertained from the patient's general practitioner was sudden collapse in three and death after admission to hospital with presumed infarction in four. An independent observer reviewing referral letters would have reassigned one of the six who died on the routine list to the urgent list. Over the past three years the procedural mortality from coronary arteriography has been 0·086%.

This audit shows a small but definite mortality among patients awaiting coronary arteriography which exceeds the risks of the procedure itself. Furthermore, these patients cannot easily be identified from clinical details at the time of referral, suggesting that this mortality can be reduced only by shortening waiting lists.

Geriatric congenital heart disease: incidence of initial presentation

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Initial presentation of congenital heart disease in elderly people is well recognised, but information on incidence is scarce. Over the past five years 3850 patients over 65 were referred to our unit for echocardiography. Nineteen (0·5%) of these presenting for the first time with symptoms and signs of cardiac disease were found to have a congenital heart defect. Patients were aged 65 to 87 years. The condition of five patients was New York Heart Association (NYHA) class I, of four class II, of eight class III, and of two class IV. Eleven were referred because of unexplained heart failure, four with a systolic murmur for clarification, and in four cases the condition had been correctly diagnosed clinically before referral. Thirteen patients were in sinus rhythm and six in atrial fibrillation. Lesions detected were: atrial septal defect (eight cases), ventricular septal defect (three), ventricular septal defect plus pulmonary valve stenosis (one), bicuspid aortic valve (three), tetralogy of Fallot (two), Ebstein's anomaly of the tricuspid valve (one), and cor triatriatum (one). Four patients, three with atrial septal defect and one with a stenotic bicuspid aortic valve, had corrective surgery and were well at follow up (the disease was NYHA class II in all cases).

A small number of patients, 0·5% of referrals to us for echocardiography, reach old age with previously undiagnosed congenital heart disease. Some lesions are complex, but despite this a considerable number (nine out of our 19 patients) are still well (NYHA classes I and II) and have only clinically mild heart failure.

Electrocardiogram interpretation in general practice

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In the United Kingdom medical prehospital coronary care is almost entirely dependent on the general practitioner (GP) service. There is currently much debate on the role of GPs in initiating thrombolysis outside hospital, thereby reducing the delay in providing this treatment to suitable patients with acute myocardial infarction (AMI). It has been recommended, however, that only general practitioners proficient in interpreting an electrocardiogram (ECG) should administer thrombolytic agents. We therefore decided to assess the current ability of general practitioners to recognise acute ischaemia in an ECG. One hundred and fifty general practitioners in the Merseyside area were selected at random and, without any warning, were approached at clinical meetings or in surgeries and asked to interpret a series of six 12 lead ECGs. Details of age, postgraduate training, and clinical practice were also requested. One hundred and six doctors (mean age 45 years) agreed to participate. Three of the six ECGs showed acute myocardial infarction, one was normal, and two showed non-acute ischaemic changes. Between 8% and 30% of general practitioners accurately diagnosed acute myocardial infarction, 82% recognised a normal ECG, and between 22% and 25% correctly interpreted non-acute ischaemia. Neither routine use of an electrocardiograph nor postregistration hospital experience in general medicine was associated with significantly greater ability to detect acute myocardial infarction in an ECG.

We conclude that at present the majority of general practitioners are not adequately proficient in interpreting acute ischaemia in ECGs.

Potential reduction in risk of sudden death by implantable defibrillators: economic implications

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The implantable cardioverter-defibrillator (ICD) is effective at preventing sudden death in patients with sustained ventricular tachycardias (VT). At present, rates of funding and implantation in the United Kingdom are severely restricted. We undertook a retrospective review of 127 patients investigated and managed for sustained VT between 1984–90 to assess the potential benefits of and requirements for ICD implantation. Patients experiencing VT within 48 hours of myocardial infarction were excluded. Eleven patients (group 1) had no sustained VT inducible at baseline electrophysiological study. Eighty five patients had inducible VT, of whom 30 (group 2) were receiving drug suppression treatment; of the 55 whose VT was still inducible, 44 had a haemodynamically tolerated arrhythmia (group 3) and 11 had a poorly tolerated arrhythmia (group 4) despite drug treatment. Empirical treatment without electrophysiological study was used in 31 (group 5). During a mean follow up of 18 months (range 0·2–76), there were 17 sudden deaths. The incidence in groups 1–5 respectively was 0%, 10%, 16%, 36%, and 10%. The number of implants required per sudden death prevented and the costs according to different policies were calculated assuming a device cost of £12 000. This would be: inducible on treatment/poorly tolerated 11/4 (£33 000), all inducible on treatment (groups 3 and 4) 55/11 (£60 000), all inducible at electrophysiological study 86/15 (£69 000), and all patients with VT 127/17 (£90 000).

Many (65%) sudden deaths could be prevented by implanting ICDs into groups 3 and 4, but at an initial cost of £660 000.

Does programmed ventricular stimulation identify patients at risk of sudden death in survivors of acute myocardial infarction?

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Programmed ventricular stimulation was performed in 90 survivors of acute myocardial infarction (range 7–14 days). A strict stepwise protocol was used involving stimulation at a single right ventricular site during sinus rhythm and three drive cycles with up to three extra stimuli. Stimulation was terminated on the induction of a sustained arrhythmia. Ten patients developed sustained monomorphic ventricular tachycardia (SMVT); 24 patients developed polymorphic ventricular tachycardia/ventricular fibrillation (PMVT) and in 56 patients no sustained arrhythmia was induced. In 25 patients non-sustained ventricular tachycardia (NSVT), defined as greater than six beats duration but less than 30 seconds, was induced. Fourteen patients with NSVT progressed to PMVT at the same or a later stage of the protocol, but no patient with NSVT progressed to SMVT. During a one year follow up there were five sudden deaths and five patients re-presented with sustained ventricular tachycardia (VT). The induction of SMVT at programmed ventricular stimulation identified all five cases of VT (sensitivity 100%, specificity 94%, positive predictive accuracy 50%) but only two cases of sudden death (sensitivity 40%, specificity 91%, positive predictive accuracy 20%). Those patients developing VT were characterised by poor left ventricular function and increased age compared with the patients who died suddenly. Although programmed ventricular stimulation failed to identify sudden death, other markers of arrhythmic risk were present in this group; three out of five had a positive signal averaged electrocardiogram and all five had frequent ventricular ectopics (> 10/h).

Programmed ventricular stimulation identifies patients at risk of developing late ventricular tachycardia rather than sudden death. PMVT is a non-specific response and can be avoided by terminating programmed ventricular stimulation if a NSVT occurs, without loss of predictive accuracy.

Heart rate variability and left ventricular ejection fraction: comparison of predictive characteristics for all cause mortality, arrhythmic events, and sudden death after myocardial infarction

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To refine postinfarction risk stratification we compared the predictive values of the heart rate variability (HRV) index (calculated as the baseline width of the histogram of RR interval durations) and the ejection fraction (EF) for all cause mortality, arrhythmic events, and sudden death in 385 survivors of acute myocardial infarction followed up for at least three months. Thirty eight (9·9%) patients died. There were 30 arrhythmic events, of which 16 were sudden deaths. A HRV index of < 305 ms had a sensitivity of 75% and a specificity of 52% for all cause mortality whereas for a sensitivity of 75% the EF had a specificity of 40%. A HRV index of < 234 ms had a sensitivity of 75% and a specificity of 76% for arrhythmic events when the EF had a specificity of only 45%. An EF of ⩽ 40% had a sensitivity of 42% and a specificity of 75% for arrhythmic events; for a sensitivity of 42% a HRV index of 156 ms had a specificity of 92%. To predict 75% of sudden deaths a HRV index of < 250 ms had a specificity of 75% and the EF a specificity of 47%. An EF ⩽ 40% had a sensitivity of 40% and a specificity of 73% for sudden death; for a sensitivity of 40% a HRV index of < 190 ms had a specificity of 83%.

The HRV index seems to be a better predictor of important postinfarction complications than the EF.

Lipid adnormalities in British Asian and white patients and in Asian patients in India with coronary artery disease

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Lipid profiles which included total cholesterol (TC), triglyceride (TGL), high density lipoprotein (HDL), apo A1, apo B, and lipoprotein (a) (Lp (a)) were measured in a consecutive series of 56 British Asian (BA) patients and 65 randomly selected white patients. These were compared with 47 BA controls and 57 white controls randomly selected from the community. Consecutive series of 28 Asian patients in India (API) were compared with 28 randomly selected Asian controls in India (ACI). All British Asian subjects had migrated from the north west of the Indian subcontinent and subjects resident in India were from the same geographical area. These groups have not previously been compared. Statistical significance was set at a conventional 5% level. TC (mmol/l) concentration was significantly higher in patients than in controls and values were lowest in subjects from India (6·5 *v* 6·0 in white controls, 6·2 *v* 5·6 in BA, and 5·5 *v* 5·1 in Asians in India). TGL concentrations were significantly higher in patients than in controls (1·88 *v* 1·29 in white controls, 2·11 *v* 1·68 in BA, and 1·92 *v* 1·39 in Asians in India). HDL was significantly lower in patients than in controls (1·09 *v* 1·28 in white controls, 1·05 *v* 1·09 in BA, and 0·89 *v* 1·24 in Asians from India). Apo A1 concentrations were similar—1·14 *v* 1·20 in white controls, 1·13 *v* 1·23 in BA, and 0·97 *v* 1·10 in Asians from India. Apo B concentrations were significantly higher in patients than in controls (1·55 *v* 1·4 in white controls, 1·42 *v* 1·09 in BA, and 1·34 *v* 1·2 in Asians from India). Lp (a) concentrations (mg/dl) were significantly higher in BA patients but not in white patients (187 *v* 114 and 180 *v* 162) and lower in API than ACI (151 *v* 170).

We conclude that Asians (patients and controls) have significantly lower TC, higher TGL, lower HDL, lower apo A1, and higher apo B concentrations than white patients and controls. British Asians have significantly higher TC and TGL than Asians in India, probably signifying the effect of environment. Lp (a) concentrations are interesting in that they are higher in BA than whites but patients had lower concentrations than controls from India.

Haemodynamic effects of total right ventricular disarticulation for ventricular tachycardia

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Total right ventricular disarticulation is a radical operation performed to control ventricular tachycardia in patients with arrhythmogenic right ventricular dysplasia (ARVD). This analysis aims at defining the acute and chronic haemodynamic impact of the operation based on five patients with histologically confirmed ARVD who had such surgery at this hospital (mean age 30 years; four male, one female). After surgery creatine kinase and creatine kinase MB activities rose to mean values of 2348 IU/l and 175 U/l respectively. Acute right heart failure was present in three patients (60%) but cleared with intravenous fluids and inotropic treatment. Echocardiographic, nuclear, and angiographic studies showed no right ventricular (RV) movement, but this was compensated for within the early postoperative period by marked paradoxical septal motion. RV end systolic dimensions rose by 41% (2·65 (0·33) to 3·39 (0·42) cm) and end diastolic dimensions by 29% (3·08 (0·37) to 4·28 (0·87) cm). Left ventricular function was preserved after surgery. Catheterisation before hospital discharge showed that RV pressure waveforms were markedly abnormal, consistent with the conduit nature of the right ventricle. Postoperatively mean right atrial pressure was 17 mm Hg. Acute renal impairment occurred in all six patients; it was worst on day 7 (mean urea 21·7 mmol/l, mean creatinine 275 μmol/l) but normal by day 18 without recourse to dialysis. The mean duration of intensive care treatment was 106 hours (range 24–408) and the mean postoperative hospital stay was 17 days (range 11–35). All patients survived surgery, returned to high functional status without diuretic treatment, and were arrhythmia free at a mean postoperative follow up of 19 months (range 2–65).

Despite the radical nature of this operation and its acute haemodynamic problems, it is effective in arrhythmia suppression and surprisingly well tolerated in the long term.

Effects of adenosine on monophasic action potential in humans

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We assessed the effects of therapeutic doses of adenosine on human atrial and ventricular repolarisation in 15 patients (11 men; aged 18–61) undergoing diagnostic electrophysiological studies. The atrial monophasic action potential (MAP) was recorded continuously during constant rate atrial pacing (cycle length 495·4 (70) ms). The MAP duration to 90% repolarisation (MAPD$_{90}$) was measured at baseline after intravenous adenosine 6 mg and 12 mg. The ventricular MAPD$_{90}$ was measured in five patients during ventricular pacing after 12 mg adenosine. After 6 mg adenosine the atrial MAPD$_{90}$ shortened from 223·1 (27·6) to 185·6 (28·3) ms ($p < 0·005$). After 12 mg the atrial MAPD$_{90}$ shortened to 168 (31·1) ms ($p < 0·001$). After 12 mg the ventricular MAPD$_{90}$ showed no significant change (247 (28·3) to 242 (27·3) ms). The magnitude of the effect on the atrium between the two doses of adenosine was significant ($p < 0·01$) as was the difference between the effect on the atrium and ventricle ($p < 0·005$). The effect on the atrium began at 10·7 (7·3) s and reached a maximum at 21·6 (7·9) s at the time of atrioventricular block or onset of symptoms.

Adenosine in therapeutic doses markedly shortens atrial but not ventricular MAPD$_{90}$ in a dose dependent manner. This may explain its tendency to provoke atrial fibrillation.

Skin blood flow in women with angina pectoris and normal coronary arteries: effects of oestrogen treatment

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Many patients with chest pain and angiographically normal coronary arteries (syndrome X) are women of perimenopausal age. Syndrome X has been shown to be associated with peripheral and coronary vasomotor dysfunction. Climacteric symptoms such as hot flushes and migraine are caused by vasomotor instability, and dyspnoea and chest discomfort may also occur perimenopausally. Such symptoms are well controlled by hormone replacement therapy. In this study evidence for peripheral vasomotor dysfunction was sought in 20 women with syndrome X and 10 age matched female controls by measuring the cutaneous hyperaemic response. The finger tip blood flow (expressed in mV) was measured by laser Doppler velocimetry after the release of five minutes of arterial occlusion. Ten of the subjects with syndrome X were treated with two months of transdermal 17β-oestradiol and then retested in a similar manner. The patients with syndrome X had a higher baseline blood flow compared with controls before treatment (751 (372) *v* 318 (270) mV, p < 0·05) and a lower maximum to baseline flow ratio after release of the blood pressure cuff (0·99 *v* 3·8, p < 0·01). After treatment a significantly lower baseline (295 (230) *v* 751 (372) mV, p < 0·002) and a significant increase of maximum to baseline ratio (2·07 *v* 1·06, p < 0·01) compared with pretreatment values were found. No significant difference in resting blood flow (295 (230) *v* 318 (270) mV, NS) or ratio of hyperaemic response maximum to baseline (2·07 *v* 2·31, NS) was found between patients after oestrogen treatment and normal controls.

Thus patients with syndrome X have a higher baseline flow and a lower maximum hyperaemic to baseline ratio compared with normal subjects. Oestrogen replacement therapy normalises peripheral blood flow in patients with syndrome X, and the potential beneficial effects on coronary flow and symptoms need to be evaluted.

Acute vasodilator response of pulmonary vascular bed in primary pulmonary hypertension

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To study the acute vasodilator response of the pulmonary vascular bed in primary pulmonary hypertension five patients (four women, mean age 34 years, range 21–45) were studied. Haemodynamic parameters were recorded at baseline (B) and after incrementally increasing intrapulmonary infusions of acetylcholine at $3{\cdot}4\times10^{-13}$ to $3{\cdot}4\times10^{-8}$ mol/min and calcitonin gene related peptide (CGRP) at 0·5 to 2×10^{-11} mol/min at five minute intervals or until a reduction in systolic systemic artery pressure of 25 mm Hg occurred. Oral nicardipine was then given at 60 minute intervals (dose range 100–200 mg). There was no significant increase in stroke volume from baseline with acetylcholine or CGRP (42 (SD 19) at baseline to 46 (23) ml with acetylcholine; 46 (23) at baseline to 50 (28) ml with CGRP), but nicardipine increased stroke volume from 34 (15) to 50 (19) ml (p < 0·05). There was no significant reduction in systolic pulmonary artery pressure with acetylcholine, CGRP, or nicardipine. Total pulmonary vascular resistance was reduced with nicardipine from 7·4 (4·9) to 4·3 (3·1) units (p < 0·05) but not with acetylcholine or CGRP. Systemic artery pressure fell from 132 (34) to 113 (36) mm Hg (p < 0·05) with CGRP and from 134 (32) to 99 (26) mm Hg (p < 0·01) with nicardipine.

Thus, despite a reversible component to the increased total pulmonary vascular resistance in primary pulmonary hypertension, infusion of acetylcholine and CGRP do not significantly reduce systemic pulmonary artery pressure or total pulmonary vascular resistance. This may be due to a defect in endothelial cell function.

New clinical index of left ventricular mechanical performance

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The conversion of energy to heat by the left ventricle (LV) myocardium is irreversible and represents inefficiency in the transformation of metabolic energy into external work. We have developed a method for the clinical measurement of LV heat production and applied it in 46 patients with chest pain (31 men, aged 37 to 72 (mean 57) years) undergoing cardiac catheterisation. Coronary artery disease was documented in 38; eight had normal coronary arteries. LV mechanical efficiency was calculated from measured LV heat production and LV energy supply (calculated from LV oxygen extraction). There was a close linear relationship between LV heat production and LV energy uptake (r = 0·92, p < 0·0005). At rest, under basal conditions, LV heat production for the whole group was 3·0 (1·4) W and mechanical efficiency was 33·1% (11·7%). LV mechanical efficiency in the normal group was 44·2% (9·7%) compared with 30·7% (10·7%) in patients with coronary disease (p = 0·004). In 27 patients atrial pacing was undertaken to alter LV energetics. LV energy supply increased in these patients from 4·6 (2·7) W to 5·9 (3·3) W (p < 0·0005), with a similar increase in LV heat production from 3·0 (1·6) W to 4·6 (2·4) W (p < 0·0005). As most of the increased energy utilisation appeared as heat rather than work, there was a significant fall in LV mechanical efficiency with pacing from 33·9% (13·5%) to 18·9% (15·2%) (p < 0·0005).

These results demonstrate that measurement of LV heat production is a practical means of characterising LV mechanical performance in the clinical setting.

Identification of patients at risk of late postinfarct ventricular arrhythmias: ventricular late potentials, Holter monitoring, and ejection fraction

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The two main aims of this study were to establish the prognostic values of ventricular late potentials (VLP), Holter monitoring, and ejection fraction (EF) in identifying patients at risk of late postinfarct ventricular arrhythmias and to determine which filter frequency (25 Hz or 40 Hz) provides the better predictor of outcome. Signal averaged electrocardiograms for VLP, measurement of EF, and Holter monitoring were performed in 211 consecutive patients with first infarcts before discharge. Over the maximum follow up period of 20 months (mean 10·8) there were nine sudden deaths and two patients presented with ventricular tachycardia. Of the 11 who had arrhythmic events (group 1), all 11 had VLP (40 Hz) compared with 45 (22·5%) of those without arrhythmic events (group 2). The figures with the 25 Hz filter were 2 (18·2%) and 15 (7·5%) respectively. Eight (72·7%) patients in group 1 and 45 (22·5%) in group 2 had couplets or salvos on Holter monitoring. Five (45·5%) patients in group 1 and 20 (10%) in group 2 had EF less than 40%. VLP (40 Hz) predicted arrhythmic events with a sensitivity of 100% and a specificity of 77·5%. The corresponding values for the 25 Hz filter were 18·2% and 92·5%; for Holter monitoring they were 72·7% and 77·5% and for EF 45·5% and 90%. Multifactor analysis identified VLP (40 Hz) and Holter monitoring as the only independent predictors of outcome. Their combination had a sensitivity of 72·7% and a specificity of 92·5%.

In conclusion, both VLP and Holter monitoring are important predictors of arrhythmic events and the 40 Hz filter provides the better predictor of outcome.

Circadian variation in white blood cell aggregation and free radical indices in healthy volunteers

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Previous studies have shown circadian rhythms in the onset of thrombotic events, which occur most commonly in the morning, and also in the fibrinolytic activity of the blood, which has a peak in the evening and a trough in the morning. There has recently been increasing interest in the role of white cells and free radicals in thrombosis. No one has yet investigated the potential circadian variation of white cell aggregation and free radicals in humans. We studied the circadian rhythm of white cell aggregation and free radical status in 10 healthy male volunteers. Six blood samples were collected at four hourly intervals from 12 midday until 8 am the following morning. The volunteers carried out normal daily activities until 12 midnight, when they went to bed, where they remained until 8 am. The following were measured in each sample: white cell aggregation; malonyldialdehyde concentration, which is a product of lipid peroxidation by free radicals; free radical scavengers; plasma thiols (PSH); red cell lysate thiols (LSH); glutathione (GSH) and superoxide dismutase (SOD) activities, which are all altered in the presence of free radical activity. The following parameters showed significant circadian rhythms: white cell aggregation (p < 0·001), malonyldialdehyde (p < 0·015), PSH (p < 0·001), LSH (p < 0·002). White cell aggregation was lowest at 9 am and highest at midnight to 4 am. Malonyldialdehyde and PSH both had a peak at 4 pm and a trough at 4 am. LSH had a peak at 12 noon and a trough at 8 am.

As the behaviour of white cells and free radical state influence the flow properties of blood, a circadian rhythm in white cell function and free radical state may contribute to the time of onset of thrombotic diseases. Moreover, with many studies being currently undertaken in this subject, our work indicates the need to standardise sample times.

Effects of captopril and of isosorbide mononitrate on ventricular arrhythmias during acute phase of myocardial infarction: randomised trial

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To assess the effects of oral vasodilator treatment on ventricular arrhythmias during the early phase of myocardial infarction 76 patients (mean age 61 (9) years) were randomised at a mean of 12 hours from the onset of pain to captopril (12·5 mg three times a day after a 6·25 mg test dose; n = 27) or isosorbide mononitrate (ISMN; 20 mg three times a day; n = 23) or placebo (n = 26). The clinical characteristics of the three groups were closely matched and 95% of the patients received thrombolysis. All patients had 48 hours of Holter monitoring starting at the time of randomisation. For each patient the number of ventricular ectopics (VE) per hour, multiplets per hour, and episodes of ventricular tachycardia (VT) were calculated for the whole 48 hour period. VE and multiplets per hour were logarithmically transformed to obtain normal distributions. The mean log VE per hour for the placebo, captopril, and ISMN groups were respectively 1·13 (SEM 0·18), 0·74 (0·14), and 0·49 (0·12) (p = 0·005 for ISMN *v* placebo, all other comparisons NS). A similar trend was seen for log multiplets per hour: 0·03 (0·16), −0·39 (0·14), and −0·59 (0·09) (p = 0·005 for ISMN *v* placebo). The frequency of episodes of VT in the active treatment groups was not significantly less than that in the placebo group: 5·5 (1·8) for placebo, 3·0 (0·9) for captopril, and 2·1 (0·7) for ISMN. During the first six hours after randomisation 42% of the placebo, 15% of the captopril, and 9% of the ISMN groups had at least one episode of idioventricular rhythm (p < 0·05 for captopril *v* placebo and p < 0·01 for ISMN *v* placebo).

In summary, these data suggest that ISMN and perhaps to a lesser degree captopril reduce the incidence of ventricular arrhythmias in the acute phase of myocardial infarction. Further study on far larger numbers is required to determine whether these effects are translated into reductions in serious arrhythmias, such as ventricular fibrillation, and death.

Autonomic nerve dysfunction in patients with silent myocardial ischaemia

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Anginal pain is thought to be mediated via cardiac sympathetic afferent nerves. The aim of this study was to examine whether patients with silent myocardial ischaemia have evidence of autonomic dysfunction. Forty two male patients with angiographic evidence of coronary artery disease and demonstrable ischaemia on 24 hour Holter monitoring with a Reynolds solid state recorder were selected. Patients were assigned to group 1 (n = 21) if they had only silent ischaemic episodes and to group 2 (n = 21) if there were any symptomatic ischaemic episodes. Both groups underwent autonomic testing using the Valsalva manoeuvre, isometric hand grip, lower body negative pressure, and cold pressor tests. Measurements of heart rate; plethysmographic forearm blood flow (FBF) and vascular resistance (FVR); and systolic, diastolic, and mean arterial pressure were made during the latter three tests. In both groups there was no significant difference in mean age or presence of systemic hypertension. During the isometric hand grip there was a significant difference between the groups in the increase in FBF (83·2% in group 1, 48·5% in group 2; p < 0·03) and reduction in FVR (35% in group 1, 20·4% in group 2; p = 0·02). Mean arterial pressure rose by a mean of 10 mm Hg in both groups. Between the first and second minute of grip, when FBF is expected to fall and FVR increase, FBF and FVR in group 1 remained unchanged but in group 2 FBF increased by 13·5% (p < 0·02) and FVR fell by 10·4% (p < 0·01). The Valsalva RR interval ratios and lower body negative pressure test parameters did not differ between the two groups, suggesting no difference in parasympathetic function. There was no difference between the two groups in the parameters measured during the cold pressor test.

These data suggest that there are differences in autonomic function in patients with pure silent ischaemia compared with those with symptomatic ischaemia.

Thrombolytic treatment for acute infarction: more good news

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The aim of this study was to determine whether treatment with intravenous streptokinase with or without oral aspirin during infarct evolution reduces the incidence of inducible ventricular tachycardia at electrophysiological study. Of 159 patients randomised to the multicentre, placebo controlled ISIS–2 study of streptokinase and aspirin in myocardial infarction, 87 underwent electrophysiological study 6–28 days later for prognostic reasons to determine their risk of late spontaneous ventricular tachycardia. Randomisation resulted in four clinically similar patient groups (streptokinase 20; aspirin 25; streptokinase and aspirin 21; both placebo 21). With an electrophysiological study protocol with $\leqslant 4$ extrastimuli only the induction of ventricular tachycardia of cycle length $\geqslant 230$ ms for $\geqslant 10$ s was considered abnormal. Antiarrhythmic drug treatment was not routinely prescribed regardless of the result of electrophysiological study. Ventricular tachycardia was induced in eight out of 46 patients treated with placebo streptokinase *v* none out of 41 treated with active streptokinase ($p < 0{\cdot}005$) and in four out of 41 patients treated with placebo aspirin *v* four out of 46 treated with active aspirin (NS). During mean follow up of 39 (9) months no patient treated with active streptokinase had spontaneous ventricular tachycardia compared with three treated with placebo streptokinase ($p = 0{\cdot}13$).

Streptokinase treatment during acute myocardial infarction markedly reduces the incidence of inducible ventricular tachycardia in infarct survivors. Aspirin has no such effect.

White cell aggregation in coronary disease

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White cell activation has been implicated in acute myocardial ischaemia, and this may be reflected in increased white cell aggregation. This ability of white cells to aggregate in response to formyl-methionyl-leucyl-phenylalanine can be compared with a standard, allowing percentage aggregation to be measured in whole blood. In 98 patients with established coronary artery disease and 24 normal subjects there were no significant differences in random samples. (Normals 43·7% (10·6%) and patients 47·9% (12 3%). Aspirin (46·7 (12·1), n = 60), β receptor blockers (47 3 (13·3), n = 54), nitrates (45·8 (12·9), n = 60), and calcium channel blockers seemed not to affect aggregation (47·1 (12·7), n = 67). In 25 patients with angiographically established coronary artery disease, aggregation increased significantly with symptom limited maximal exercise (53·0 (9·6) to 58·6 (8·3) at peak, $p < 0{\cdot}01$) and had returned towards baseline at 10 minutes after exercise. In patients with chest pain (n = 9) as the limiting symptom aggregation increased significantly by 19% compared with 8% in patients limited by breathlessness or leg fatigue.

These results suggest white cell aggregation may be induced in response to cardiac ischaemic pain and that this may be relevant in patients with acute ischaemic syndromes.

Cardiac structure and function in postmenopausal women: effects of long term oestrogen replacement therapy

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Anxiety concerning possible deleterious cardiovascular effects of long term oestrogen therapy has been replaced by recent reports suggesting a potential cardioprotective role for hormone replacement therapy. There are, however, few studies documenting the long term effects of hormone replacement therapy on cardiac structure and function. As part of a randomised single blind study 49 women who had been taking either oestrogen treatment (n = 26) or matching placebo (n = 23) for at least 10 years underwent non-invasive cardiovascular assessment including echocardiography and exercise testing. The two groups were matched at baseline for age, arterial pressure, and body mass index. After treatment for 12–21 years bone mineral density was, as expected, significantly higher in the oestrogen treated group than in the controls (114·2 (3·5) *v* 88·9 (2·9), $p < 0{\cdot}0001$). On echocardiography left ventricular end systolic dimension was significantly lower in the active treatment group than in the placebo group (26·2 (0 9) *v* 29·9 (1 5) mm, $p < 0\ 05$) and fractional shortening significantly greater (37·6% (1·8%) *v* 31·7% (2·3%), $p < 0\ 05$). Left ventricular mass was slightly, but not significantly, lower in the oestrogen treated group (195 (9) *v* 213 (15) g, NS). Blood pressures were similar in the two groups. During treadmill exercise testing there were no differences between the two groups in terms of exercise time, development of chest pain, and maximum ST segment depression.

Thus long term oestrogen treatment does not seem to be associated with adverse cardiovascular adaptations and may have beneficial effects on cardiac structure and function.

Hyperinsulinaemic response in chronic heart failure is significantly improved by captopril

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We have shown that patients with chronic heart failure show a markedly hyperinsulinaemic response to a 75 g oral glucose tolerance test. Captopril has been shown to improve insulin sensitivity in patients with hypertension. We present the first report of the effect of angiotensin converting enzyme inhibition with captopril on hyperinsulinaemia in chronic heart failure. Twenty three non-diabetic patients (18 men, mean age 60 years) with chronic heart failure (New York Heart Association class III) were studied. At baseline all were taking frusemide (40 mg, n = 12; 80 mg, n = 11) and the dose was not changed. Mean ejection fraction was 20% (range 10–36%) and mean body mass index 25·5 (SEM 0·7) kg/m^2. A 75 g oral glucose tolerance test was performed before and four weeks after the introduction of captopril 75 mg daily. Blood samples were taken at 0, 30, 60, 90, and 120 minutes for measurement of plasma concentrations of glucose, insulin, and non-esterified fatty acids (NEFA). Fasting values of plasma glucose, insulin, and NEFA were unchanged between baseline and after four weeks of treatment with captopril. Plasma insulin concentration fell from 94 (11) mU/l 120 minutes after glucose in the baseline study to 67 (8) mU/l after the introduction of captopril ($p < 0·01$). There was no significant change in plasma concentrations of glucose (7·4 (0·7) *v* 6·9 (0·45) mmol/l) or NEFA (62 (12) *v* 91 (34) μmol/l) at 120 minutes.

Captopril significantly decreases the late hyperinsulinaemic response to an oral glucose load in patients with chronic heart failure. This effect of captopril is not mediated by a reduction in circulating concentrations of NEFA. Hyperinsulinaemia is associated with sodium retention and impaired muscle metabolism and a reduction in insulin concentrations may correspond to an improvement in clinical wellbeing.

Controlled trial of magnesium supplementation in congestive heart failure: effects on electrolytes, arrhythmias, haemodynamics, and sympathetic activity

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Magnesium depletion is often present in congestive heart failure and may exacerbate hypokalaemia, arrhythmias, peripheral vasoconstriction, and neurosympathetic activation. The effects of magnesium supplementation were investigated by a randomised double blind crossover trial in 12 patients with chronic congestive heart failure (New York Heart Association classes II–IV) and frequent (>500/24 h) ventricular ectopic activity who were all taking long term loop diuretic treatment. Subjects alternately received enteric coated magnesium chloride ($MgCl_2$) (magnesium 17 mmol/day) or placebo for six weeks. Treatment was well tolerated, but one patient withdrew because of dyspeptic symptoms. Compared with placebo, $MgCl_2$ increased urinary magnesium excretion from 2·93 (1·26) to 4·77 (2·01) mmol/24 h ($p < 0·01$), but there was no significant rise in serum concentrations of magnesium (0·88 (0·08) *v* 0·92 (0·06) mmol; NS) or potassium (3·9 (0·4) *v* 4·1 (0·2) mmol; NS). $MgCl_2$ produced significant suppression of asymptomatic ventricular arrhythmias: mean (range) ventricular ectopic frequency was reduced from 4537 (654–14 573) to 3630 (184–10 964)/24 h (p = 0·05), couplets from 261 (5–1572) to 160 (1–1038)/24 h ($p < 0·02$), and episodes of ventricular tachycardia from 57 (0–378) to 17 (0–121)/24 h ($p < 0·05$). There was no difference between placebo or $MgCl_2$ with regard to mean arterial pressure (91 (10) *v* 88 (9) mm Hg; NS), cardiac index (2·31 (0·47) *v* 2·20 (0·46) $l/min/m^2$; NS) and systemic vascular resistance (1635 (541) *v* 1656 (510) dynes × s/cm^5; NS), and there was no change in plasma concentrations of noradrenaline (546 (136) *v* 592 (220) pg/ml; NS) and adrenaline (605 (732) *v* 203 (113) pg/ml; NS).

In conclusion, magnesium supplementation resulted in suppression of ventricular ectopic activity, particularly repetitive forms, but did not improve haemodynamics or neurosympathetic indices.

Aortic balloon pumping in cardiogenic shock: effects on cardiac output, renal blood flow, and renal oxygen consumption

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The effect of aortic balloon pumping on renal perfusion during cardiogenic shock has not been reported in humans. We have developed and validated a portable continuous thermodilution method for direct measurement of renal blood flow that allows rapidly repeatable measurements to be taken. In vitro blood flow was measured against known flow rates in a cardiopulmonary bypass circuit with excellent correlation (R = 0·99) over the full range of renal blood flows normally encountered in humans (95–1024 ml/min, mean difference 39 (64) ml/min, maximum error observed 13%). In vivo left renal blood flow was measured serially in nine pigs by simultaneous renal vein thermodilution and renal artery electromagnetic flow probe before and after induction of shock (difference between methods 23 (40) ml/min, R = 0·92). Cardiac output, mean arterial blood pressure, left renal blood flow, and left renal oxygen uptake were measured in seven patients in cardiogenic shock (cardiac index <2·5, mean 1·7 (0·4)) with aortic balloon pumps in situ. Cardiac output was 3·4 (0·8) l/min during 1:1 aortic balloon pumping and 3·0 (0·9) l/min measured after the balloon had been switched to standby for 15 minutes ($p < 0·02$). However, there was no significant difference in mean arterial blood pressure (70 (6) mm Hg in 1:1 *v* 69 (13) in standby), left renal blood flow (210 (124) ml/min in 1:1 *v* 197 (127) in standby), or left renal oxygen uptake (5·0 (3) ml/min in 1:1 *v* 5·0 (2) in standby).

The renal vein continuous thermodilution technique permits rapid, direct measurement of renal blood flow in patients with cardiogenic shock and is of potential value in guiding treatment directed at increasing renal perfusion. Despite achieving a small but significant increase in cardiac output aortic balloon pumping did not increase renal perfusion or oxygen consumption in this group of patients with renal hypoperfusion and low cardiac output.

Detection of myocardial perfusion by intravenous contrast digital radiofrequency echocardiography

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Conventional contrast echocardiography techniques have proved inadequate for the detection of myocardial perfusion with the new intravenously injected echocardiography contrast agents because of the limitations and relative insensitivity of standard echocardiographic equipment. To avoid these problems we have used a modified phased array ultrasound scanner and an on line computer system to obtain pure digital radiofrequency ultrasound (DRF) data (derived from the transducer preamplifiers) from the left ventricle and myocardium during intravenous contrast myocardial perfusion echocardiographic studies. In 10 patients after coronary arteriography intravenous injections of the echocardiography contrast agent Albunex (sonicated human serum albumin) in two doses of 0·08 and 0·22 ml/kg were given during DRF echocardiography. The DRF data were successfully obtained and analysed in seven patients for a shift in the frequency spectrum which could be caused by resonance of the Albunex contrast microbubbles in the heart—a phenomenon that has been previously shown in vitro. The mean integrated backscatter (MIB, a measure of the total ultrasound energy) was also calculated before, during, and after Albunex injection. In segments where perfusion was predicted to be normal there was a significant increase in MIB from 0·89 to 1·93 units ($p < 0·02$) and time intensity curves could be constructed showing wash in and out of contrast from the myocardium. Peak contrast intensity in the myocardium was delayed by a mean of six beats from peak left ventricular intensity. In four segments where very poor perfusion was predicted MIB intensity increased by only 7% and wash out was prolonged. In all myocardial segments contrast microbubble resonance also caused a drop in mean frequency of 140 kHz ($p < 0·005$) and permitted similar temporal analysis of myocardial perfusion. Frequency changes preceded intensity changes in both the left ventricle and myocardium by 2·3 beats and represent faster pulmonary transmit of smaller contrast microbubbles.

In conclusion, this study shows for the first time that DRF echocardiographic analysis provides a method of detecting myocardial perfusion after intravenous Albunex.

Coronary artery ultrasonography with 7·5 MHz transducer: comparison with histopathology

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High frequency epicardial echocardiography (HFEE) is a technique that directly images the coronary artery by epicardial placement of an ultrasound transducer. It may therefore provide information intraoperatively supplementary to coronary angiography. The purpose of this study was to assess the accuracy and reproducibility of the technique in locating coronary arteries, measuring dimensions, and identifying atherosclerotic lesions. Five pressure perfused postmortem human hearts were studied with a 7·5 MHz Vingmed/Sonotron transducer and comparison made with histopathological examination. Twenty two coronary arteries were imaged, luminal diameter range 0·9–0·5 mm. There was close agreement between ultrasound and pathological measurements of luminal diameter ($r = 0·99$, $p < 0·0001$, $n = 26$). Intraobserver and interobserver variability measurements showed excellent reproducibility, the coefficient of variation being 3·95% and 3·8% respectively. The resolution of the transducer was not high enough to measure wall dimensions accurately but could readily identify diffuse wall thickening and calcification. HFEE was accurate in identifying atherosclerotic lesions, imaging arteries distal to an occlusion, locating deeply sited arteries, and identifying complete obliteration of an artery.

HFEE may therefore provide valuable information intraoperatively. Cardiac movement and restricted access may pose difficulty to the in vivo use of HFEE. However, with video playback facilities and transducer miniaturisation the intraoperative assessment of coronary artery disease may become a real possibility.

Quantitation of spatial velocity characteristics in hypertrophic cardiomyopathy: on line digital analysis of colour Doppler flow map images

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Digital computer analysis of colour Doppler flow mapping can provide quantitative spatial velocity information. We studied 14 patients with hypertrophic cardiomyopathy by using a Vingmed CFM750 with a 3·5 MHz transducer. Images were obtained in the velocity variance mode with low pulse repetition frequency and moderately high gain. On line digital data transfer was performed to an Apple IICi computer, with maximum outflow tract velocity estimated from the spatial change in velocity on colour flow mapping. The computer digitised data were then subjected to multiple alias unwrapping, yielding velocities ranging from 0·94–5·6 m/s which correlated well with continuous wave Doppler velocities (0·98–5·7 m/s, $r = 0·95$). The site of maximum velocity on colour flow mapping occurred at the point of maximum systolic anterior mitral valve motion in all patients. In five patients with significant systolic obstruction high levels of variance occurred in the subaortic region distal to anterior mitral motion (average pixel variance 35% *v* 2% in patients with no obstruction). One patient with a subaortic muscle shelf but no obstruction had a very small associated area of high variance but a normal averaged outflow tract variance value. Spatial acceleration (in cm/s per cm) proximal to the site of maximum obstruction was quantified from the spatial change in velocity. The maximum rate of spatial acceleration occurred just proximal to systolic mitral motion and in the five patients with obstruction was >240 cm/s per cm compared with <70 cm/s per cm in the nine patients with no obstruction.

Digital data analysis of colour flow map images can quantitate velocities, spatial acceleration, and the presence and extent of disturbed flow in hypertrophic cardiomyopathy and can provide important functional insights into the flow dynamics and obstructive characteristics in such patients.

Myocardial infarction with complete heart block treated with thrombolysis

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Acute myocardial infarction is complicated by complete heart block in 7–11% of cases, most often complicating inferior myocardial infarction. Thrombolytic treatment has frequently been withheld from patients with complete heart block after myocardial infarction because of the presence of significant hypotension and the risk of bleeding should temporary pacing be required. Nevertheless, successful coronary thrombolysis results in improvement in perfusion of the conduction system. We treated 21 patients (12 male, nine female) with thrombolysis for acute myocardial infarction (20 inferior myocardial infarction) complicated initially by complete heart block; two patients had had a previous myocardial infarction. Thrombolytic treatment was started at a mean of 154 minutes after the onset of symptoms, and 12 patients received prehospital thrombolysis. All patients had previously received intravenous atropine. Of the 12 who remained in complete heart block at the time of receiving the thrombolytic agent, 10 reverted to 1:1 atrioventricular conduction and one to chronic atrial fibrillation within two hours of treatment. Only four patients required temporary transvenous pacing. Coronary artery patency during the hospital stay was 15/19 (79%) and the mean global left ventricular ejection fraction was 57% (10%) by radionuclide ventriculography. No haemorrhagic complications occurred. Ventricular fibrillation occurred in four patients during the first 24 hours after myocardial infarction. Late ventricular fibrillation occurred in one patient during reinfarction 15 days after thrombolytic treatment. Only one patient with an anterior myocardial infarction and cardiogenic shock died.

Thus thrombolysis for myocardial infarction complicated by complete heart block is a safe procedure that frequently results in resumption of normal conduction, reducing the need for pacing and improving prognosis.

Study of force interval relations in atrial fibrillation in humans

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Beat to beat variations in the pulse during atrial fibrillation have conventionally been attributed to time dependent changes in filling. I explored the alternative possibility that they are dependent on the intrinsic myocardial interval force relation. Left ventricular contractility (peak rate of rise of pressure ($\mathrm{LVdP/dt_{max}}$)) and the aortic velocity integral, which is related to stroke volume, were measured during cardiac catheterisation in 12 patients with atrial fibrillation. Within the range of intervals that determine the interval force relation a positive relation was found between preceding interval, measured from the electrocardiogram (ECG), and contractility-mechanical restitution, and an inverse relation was found between pre-preceding interval and contractility-postextrasystolic potentiation. The variations in contractility contributed significantly to the variations in the aortic velocity integral. These relations were confirmed in the patients during pacing protocols which introduced single extrasystoles into steady state pacing. ECG sequences were borrowed from three of the patients with atrial fibrillation to drive isometrically contracting isolated guinea pig papillary muscle and postextrasystolic potentiation was again found. The maximum rate of rise of force in the isolated muscle correlated well with $\mathrm{LVdP/dt_{max}}$ in the patients.

I conclude that interval force mechanisms contribute significantly to the characteristic beat to beat variation of the pulse found in atrial fibrillation.

Endocardial modulation of myocardial contraction

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Recent experiments with isolated heart muscle preparations have shown that endocardium can influence contraction of underlying myocardium by analogy with the role of vascular endothelium in regulating blood vessel tone. Selective endocardial damage abbreviates the duration of contraction—a novel "inotropic" effect which differs from that of other interventions and carries pathophysiological implications particularly for early diastolic filling. This study addresses predominantly the mechanisms underlying the influence of endocardium on myocardial contraction. Experiments with isolated muscle and a newly developed endocardial cell culture preparation show that endocardial cells release two humoral agents which have opposing effects on myocardial contraction: (*a*) an unidentified contraction prolonging factor ("endocardin") and (*b*) a contraction abbreviating factor, which seems to be endothelium derived relaxing factor, is released both basally and in response to specific stimuli, and acts by raising myocardial cyclic guanosine phosphate concentration.

Left ventricular energetics: heat production by human hearts

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Left ventricular heat production represents inefficiency in the transformation of metabolic energy into left ventricular work. Human left ventricular heat production was estimated in 64 patients (46 male, 18 female, mean age 54·2 years) from coronary blood flow, coronary arteriovenous temperature difference, and the areas under thermodilution curves recorded in the aorta and coronary sinus after injection of cold saline into the pulmonary artery. Left ventricular mechanical efficiency was derived from heat production and the energy value of myocardial oxygen utilisation. Left ventricular heat production correlated well with substrate utilisation ($r = 0{\cdot}91$, $p < 0{\cdot}0005$). Under basal conditions heat production was 3·0 (1·5) W and mechanical efficiency was 30·5% (11·5%). Left ventricular heat production was higher and mechanical efficiency lower in patients with cardiac diseases and transplanted hearts than in patients with normal hearts. In 32 patients atrial pacing was undertaken to alter left ventricular energetics. Left ventricular energy supply increased from 4·9 (2·6) W to 6·3 (3·3) W ($p < 0{\cdot}0005$); heat production increased (3·3 (1·7) W to 5·0 (2·5) W, $p < 0{\cdot}0005$), but mean external power was not altered. Consequently, left ventricular mechanical efficiency fell from 32·8% (13·1%) to 17·9% (14·5%) ($p < 0{\cdot}0005$).

These experiments represent the first time that total energy flux has been assessed in intact human hearts.

Coronary vasodilator myocardial perfusion scintigraphy: ischaemia or redistribution? A controversy revisited

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Myocardial perfusion scintigraphy with coronary vasodilators is invaluable for the detection of coronary artery disease in patients unable to exercise. Controversy exists about whether the mechanism of differential radiotracer uptake is based on ischaemia or merely redistribution. The infrequent occurrence of electrocardiographic changes supports the latter as the principal mechanism. To appraise the incidence and severity of ischaemia we combined recordings of a more sensitive electrophysiological marker of localised ischaemia—namely, monophasic action potentials (MAPs)—with dipyridamole perfusion scintigraphy. The duration of the MAP shortens in response to ischaemia. After routine coronary angiography single site MAP recordings were obtained from the left or right ventricular endocardium, or both, in 31 patients (50 recording sites) during intravenous infusion of dipyridamole (0·015 mg/kg/min for 4 minutes). Heart rate was held constant with atrial pacing at 20% above the patient's resting rate. Technetium-99m methoxy-isobutyl isonitrile was administered four minutes after dipyridamole and single proton emission computed tomography imaging performed an hour later. Rest images were obtained the following day (two day, two dose protocol). Based on perfusion characteristics and coronary anatomical data for the MAP recording site, recordings were grouped into group 1, areas with a normal perfusion pattern (n = 30); group 2, areas with a perfusion defect without angiographic collateralisation (n = 10); and group 3, areas with a perfusion defect with angiographic evidence for collateral supply (n = 10). Shortening of the MAP duration was apparent in 18 of the 20 recordings from areas of abnormal perfusion. Mean (SEM) values for alteration in MAP duration between control and peak effect at eight minutes were 276·5 (5·3) to 274·5 (5·4) ms in group 1 (NS), 289·6 (4·7) to 278·4 (4·8) ms in group 2 ($p < 0·002$), and 269·6 (5·8) to 242 (4·4) ms in group 3 ($p < 0·0001$). ST segment shift in the electrocardiogram was evident in only eight of the 29 patients with significant coronary stenoses; these eight patients had collateralised viable areas of myocardium.

Our data povide strong evidence for myocardial ischaemia being an integral part of coronary vasodilator perfusion scintigraphy. Ischaemia is of greater intensity and more likely to be overt when myocardial viability is dependent on collateral circulation. The paucity of electrocardiographic changes may be due to the relative insensitivity of the electrocardiogram to early and localised ischaemia.

Asymmetry of cardiac sympathetic innervation in patients with ventricular tachycardia in "clinically normal" hearts shown by iodine-123 *m*-iodobenzylguanidine scanning

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Autonomic influences seem to be important in the genesis of ventricular tachycardia (VT), and these may be particularly important in patients in whom VT is exercise-induced. *m*-Iodobenzylguanidine (MIBG) is an analogue of noradrenaline which is taken up by sympathetic nerve terminals, allowing their visualisation. This study examines the regional distribution of the myocardial sympathetic nerve supply in patients with VT, in "clinically normal" hearts, and in control subjects with iodine-123 MIBG scanning. Thirty one patients were studied, of whom nine had exercise induced VT and eight VT unrelated to exercise; they were compared with six subjects with atrioventricular re-entrant tachycardia and eight patients with angiographically normal left ventricular function, normal coronary arteries, and thallium scans without evidence of reversible or fixed perfusion deficits. Single proton emission computed tomography γ scanning was performed in patients immediately and three hours after intravenous injection of $170\,\text{mBq/m}^2$ MIBG. The delayed (three hour) left ventricular MIBG uptake data were processed into bull's eye target plots with the IGE Star system, and symmetry of uptake was examined around the vertical diameter. Patients with VT had a higher proportion of asymmetrical MIBG scans (9/17 (53%)) than subjects in the control groups (0/14) ($p < 0·01$). The number of patients with asymmetrical scans among those with exercise induced VT did not differ from that among those without exercise induced VT (6/9 *v* 3/8). This suggests that patients with VT may have relative sympathetic denervation of the septal portion or less commonly the lateral wall of the left ventricle, leading to an imbalance of the sympathetic supply to the myocardium and locally imbalanced sympathetic-parasympathetic interactions.

Our results suggest that selective denervation of the human myocardium may be an important mechanism predisposing to VT in clinically normal hearts.

Dobutamine/thallium myocardial perfusion tomography

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Many factors may prevent a patient performing adequately during exercise testing. While dipyridamole induced coronary arterial dilatation serves as a good alternative during thallium myocardial perfusion imaging, it is difficult to relate abnormalities to levels of exercise achieved in everyday life. Other problems are its variable duration of action and the side effects of peripheral vasodilatation. We therefore examined the use of dobutamine for the manipulation of myocardial oxygen demand in the assessment of coronary artery disease by thallium myocardial perfusion tomography. We studied 50 patients with angina and abnormal exercise electrocardiograms before coronary arteriography. Dobutamine was infused in increasing doses from 5-20 μg/kg/min until limited by symptoms. Thallium emission tomograms were acquired immediately after and four hours later. Forty patients had significant coronary artery disease, of whom 39 (97%) had abnormal thallium tomograms. Sensitivity was higher for left anterior descending (92%) and right coronary (91%) lesions than for left circumflex lesions (83%). Ten patients had normal coronary arteries, of whom eight had normal thallium tomograms (specificity 80%). Dobutamine increased the systolic blood pressure and the heart rate, with a mean increase of 107% in the double product at 20 μg/kg/min.

The tolerated dobutamine dose was significantly correlated with the treadmill exercise time. No important arrhythmias were seen.

Dobutamine is a safe and well tolerated agent for the manipulation of myocardial oxygen demand. It is highly effective in the assessment of myocardial perfusion in patients with coronary artery disease. The relation between the achieved dose and treadmill exercise performance increases its value in the clinical assessment of patients with chest pain.

Is an abnormal exercise ejection fraction response on medical treatment of prognostic significance in coronary artery disease?

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To evaluate the role of exercise first pass radionuclide ventriculography (RNV) in the prognostic assessment of medically treated coronary disease 54 patients (mean age 57) were studied prospectively after coronary angiography. Ejection fraction (LVEF) was measured by RNV with the Scinticor system without anti-ischaemic treatment at a mean of 5·6 weeks after angiography; 32 patients with abnormal results had further RNV while receiving treatment 4·2 weeks later. At nine month follow up 10 of the 54 patients (19%, group I) had suffered adverse events (one death, one myocardial infarction, one percutaneous transluminal coronary angioplasty, two coronary artery bypass grafting, five unstable angina) and 44 were event free (group II). There was no difference between groups I and II in age, proportion with previous myocardial infarction or positive exercise ECG, number of diseased vessels, or exercise LVEF whether without (37% *v* 43%) or with anti-ischaemic treatment (43% *v* 43%). Group I tended to show a greater fall in LVEF from rest to exercise without treatment (mean 8% *v* 3%, p = 0·05). However, with anti-ischaemic treatment there was a highly significant difference in mean LVEF response to exercise between groups I and II (fall of 10% *v* rise of 3%, p = 0·0006, 95% confidence interval 19 to 6).

These results suggest that a persistent abnormal exercise LVEF response despite medical treatment predicts an adverse short term outcome in medically treated coronary disease and may improve patient selection for prognostic revascularisation.

Comparison of same day and separate day injection protocols for myocardial perfusion single proton emission computed tomography with technetium-99m methoxy-isobutyl isonitrile

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Although thallium-201 remains the most common radiotracer for myocardial perfusion scintigraphy, it is not an ideal agent and in recent years interest has focused on technetium-99m labelled compounds, notably ^{99m}Tc methoxy-isobutyl isonitrile (MIBI). Unlike thallium-201, ^{99m}Tc MIBI undergoes minimal myocardial redistribution so two injections (rest and exercise) are required, the optimum timing and activities of which have yet to be established. To clarify this problem one of three dose administration protocols for ^{99m}Tc MIBI was randomly allocated to each of 45 consecutive patients undergoing investigation for chest pain. The three regimens were 300 MBq at rest and 500 MBq 24 hours later on exercise (scheme A); 200 MBq at rest followed by 1000 MBq one and a half hours later on exercise (scheme B); 200 MBq at rest and 600 MBq one and a half hours later on exercise (scheme C). According to symptoms and the results of exercise testing and coronary angiography, patients were allocated by a single observer to one of two clinical groups: "high probability" or "low probability" of ischaemic heart disease. Images obtained from ^{99m}Tc MIBI were reported blind by two experienced observers and Cohen's κ statistic was used to measure the agreement between imaging and clinical diagnoses. Only for the separate day protocol was κ significantly greater than zero at 0·78 (95% confidence interval 0·55 to 1·01). For scheme B κ fell to 0·35 (0·12 to 0·58) and for scheme C to 0·36 (0·13 to 0·59). The degree of agreement between clinical and imaging diagnoses was significantly better for the separate day than for the same day protocols (p < 0·003) whereas schemes B and C did not differ (p = 0·99). This difference was explained by significantly fewer false negatives with scheme A. In patients clinically diagnosed as having a high probability of ischaemia only one out of seven was normal compared with nine out of 15 when B and C were combined.

This study shows that despite the incovenience to patients, exercise and rest images must be performed on separate days if myocardial perfusion scintigraphy is performed with ^{99m}Tc MIBI.

Quantitative indium-111 antimyosin antibody imaging for predicting age of acute myocardial infarction

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Myocardial uptake of indium-111 antimyosin antibody may occur in the necrotic site for prolonged periods after a myocardial infarction, resulting in difficulty in distinguishing acute from remote events. The uptake intensity may be related to infarct age and may allow more accurate interpretations of antimyosin images. We therefore studied the heart-lung ratio (measured as the ratio of the maximum counts in the infarcted myocardium to the adjacent lung background) in 90 consecutive patients at various intervals after an acute Q wave infarction. Imaging was performed 24 hours after injection of indium-111 antimyosin. In the infarct group 107 studies were performed on the 90 patients between four hours and 270 days after infarction. The heart-lung ratio was inversely correlated with the age of the infarct, with 47% of the variance being explained by age (p < 0·001). Sequential antimyosin imaging was performed in nine patients. The heart-lung ratios were (mean (SD)) 1·77 (0·25) for images between four and 15 days, 1·54 (0·12) for images between 50 and 100 days (p < 0·02), and 1·42 (0·16) (p < 0·05) for images between 125 and 270 days, confirming the inverse relation with age. A heart-lung ratio above 1·9 had 93% specificity and an 82% sensitivity for acute myocardial necrosis and may be used to distinguish acute from remote infarction.

Reduced skeletal muscle protein synthesis in chronic heart failure

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Effort intolerance, muscle weakness, and muscle wasting commonly occur in advanced heart failure. We have investigated protein synthetic rates of quadriceps muscles in vivo with stable isotope techniques. We studied seven men with left ventricular dysfunction (New York Heart Association class IIB; patients' mean age 58 years (range 46–68) and mean weight 69 kg (60–75 kg)) and compared the results with those from 25 control subjects (mean age 45 years (19–82), mean weight 74 kg (53–105)). L-[1-^{13}C] leucine was infused after an overnight fast over a seven hour period to achieve steady state plasma leucine labelling, after which a percutaneous biopsy specimen was taken from the quadriceps muscle. Muscle protein synthesis (k_s) was calculated by comparing ^{13}C leucine enrichment of muscle with that of the plasma measured by gas chromatography mass spectrometry. Muscle DNA concentration was significantly higher in the patients (3·76 (0·55) μg/mg protein) than the controls (2·04 (0·89), p < 0·01). Mean muscle protein synthesis (k_s) was 0·033 (SD 0·010)%/h in the patients compared with 0·045 (0·015) in control subjects (p < 0·01). Muscle RNA activity—that is, protein synthetic rate per RNA, which gives an index of the efficiency of protein synthesis—was 0·08 (0·03) μg of protein/h/μg of RNA in the patients compared with 0·018 (0·08) in control subjects (p < 0·05).

In chronic left ventricular dysfunction, even in the absence of clinically overt muscle wasting, there is a substantial depression (27%) of skeletal muscle protein synthesis.

Evidence of instability of circulatory regulation in patients with chronic heart failure obtained from ambulatory pulmonary artery pressure recordings

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Cardiovascular reflexes that maintain circulatory homoeostasis are abnormal in chronic heart failure. After severe insults to the circulation low frequency vasomotor waves of 0·016 to 0·083 Hz, which represent underdamping of circulatory regulatory mechanisms, have been observed. Ambulatory pulmonary artery pressure measurement with a micromanometer tipped catheter was used to detect such oscillations in heart failure. Spontaneous, sustained low frequency oscillations of pulmonary artery pressure were observed in eight patients (mean age 58 years, range 45 to 67 years) with moderate to severe chronic heart failure (mean maximum rate of oxygen consumption 14·8 ml/kg/min; mean left ventricular ejection fraction 23%) during pulmonary artery pressure recordings of 8·6 h to 48 h duration. These oscillations (frequency range 0·015 to 0·035 Hz) had a distinct peak form and a lower frequency range than respiration (0·2 to 0·6 Hz) and heart rate (0·8 to 1·9 Hz). They were present from 42% to 82% of the recording time, with an amplitude varying from undetectable to a maximum range from 5·3 mm Hg to 19·7 mm Hg. When detectable, the mean amplitude of the low frequency oscillations of pulmonary artery pressure ranged from 1·2 (SD 1·2) mm Hg to 4·3 (3·3) mm Hg.

These vasomotor oscillations are evidence for instability of circulatory control in patients with chronic heart failure. At times this control mechanism is markedly underdamped. This finding of circulatory instability may have important implications for the treatment of heart failure which might be aimed at manipulating circulatory control parameters back into the normal range.

Effects of infarct size and physical training on skeletal muscle metabolism in experimental heart failure in rats

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The influence of myocardial infarction and physical deconditioning on skeletal muscle metabolism was studied by phosphorus-31 magnetic resonance spectroscopy (MRS) in female Wistar rats 12 weeks after coronary artery ligation (n = 22) or sham operation (n = 10). Infarcted rats were allocated randomly to either six weeks training (n = 11; treadmill exercise at 15 m/min for 30 min/day, 6 days/week) or non-training (n = 11). ^{31}P spectra were collected from the calf muscle during sciatic nerve stimulation (1 Hz) both supramaximally and submaximally to produce 200 g tension. Enzymatic assays were performed on the contralateral non-stimulated leg for glutamate pyruvate transferase (enzyme favouring the removal of pyruvate) and the mitochondrial oxidative enzymes citrate synthase and β-hydroxyacyl coenzyme A dehydrogenase. Rats were divided into congestive (C) and non-congestive (NC) groups by lung to body weight ratio as an index of severity of heart failure. Changes in creatine kinase activity (CK) were expressed as CK/CK + inorganic phosphate and pH was calculated from the chemical shift of inorganic phosphate (Pi). At 200 g tension the C non-trained rats when compared with the trained C or NC sham operated or NC non-trained rats produced more acid (6·93 (0·03) *v* 7·01 (0·01), 7·0 (0·01), 6·99 (0·01), 6·97 (0·02), p < 0·05) and had lower CK/CK + Pi (0·49 (0·06) *v* 0·67 (0·04), 0·71 (0·02), 0·71 (0·04), and 0·72 (0·04), p < 0·01, ANOVA). At maximal tension the pH in C non-trained rats was significantly lower than that in all the other groups (6·86 (0·04) *v* 6.96 (0·01), 6·96 (0·02), 6·96 (0·4), and 6·96 (0·01), p < 0·01, ANOVA), while the fall in CK/CK + Pi showed a similar trend to the 200 g data but was not significant. The C non-trained group had significantly lower citrate synthase activity in skeletal muscle compared with trained C or NC and sham groups (18·3 (0·8) *v* 24·9 (0·7), 23·5 (1·8), and 25·9 (1·2) U/gww respectively, p < 0·001, ANOVA). There was a significant increase in glutamate pyruvate transferase activity in the training compared with non-training group (7·9 (0·35) *v* 6·5 (0·36) U/gww, p < 0·03, ANOVA). There were no differences in β-hydroxyacyl coenzyme A dehydrogenase activity.

The excessive CK depletion, acidification, and the reduction of mitochondrial enzymes in skeletal muscle of chronic heart failure depend on both physical deconditioning and congestive failure; training may prevent these changes.

Recovery of impaired endothelium dependent vasodilatation in atherosclerotic coronary arteries

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Hypercholesterolaemia and atherosclerosis are reported to be associated with impaired endothelium dependent vasodilatation in coronary arteries. We used a model of human familial hyperlipidaemia, the Watanabe hereditable hyperlipidaemic rabbit (WHHL), to examine long term changes in the coronary responses to endogenous vasodilators during the development of atherosclerosis. This genetic model lacks receptors for low density lipoprotein, has a consistently raised plasma cholesterol concentration (20 mmol/l), and develops early coronary atherosclerosis by 12 months of age. Isolated coronary ring preparations from 22 WHHL aged 4, 6, and 12 months and from 19 age matched New Zealand white controls (NZW) were constricted with 30 mM potassium chloride; the mean tension generated was no different in the two groups. Responses to the endothelium dependent vasodilator substance P (10^{-7} M) were found to be markedly depressed in the four month old WHHL (2·1% (1·0%)) compared with the age matched NZW (48·5% (9·9%), p < 0·001), but there were no significant differences in the relaxant responses to the smooth muscle vasodilators calcitonin gene related peptide (CGRP, 2·6 × 10 M; 74·0% (3 3) in WHHL *v* 74·9% (4·7) in NZW); vasoactive intestinal polypeptide (3 × 10^{-7} M; 52·3% (5·9) in WHHL *v* 60·6% (7·1) in NZW); and noradrenaline (10^{-4} M; 78·2% (3·4) in WHHL *v* 71·8% (6·1) in NZW). As the animals matured maximal relaxation to noradrenaline was unaffected while relaxation to CGRP and vasoactive intestinal polypeptide declined in the WHHL; the changes seen in the NZW were very similar. In contrast, relaxation to substance P in the WHHL increased significantly between four and 12 months of age (p < 0·01) while in NZW the response to substance P declined significantly over the same period (p < 0·005); by 12 months there was no difference between the two groups. Relaxation to ATP, which acts both directly on the smooth muscle and via the endothelium in this vessel, also declined significantly with age in the NZW (p < 0·05) but showed no fall in the WHHL.

These results show that impaired endothelium dependent responses in coronary arteries are capable of long term compensatory recovery during the development of atherosclerosis.

Lack of variation in venous tone in patients with malignant vasovagal syncope

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In the malignant vasovagal syndrome patients seem to develop low ventricular volumes that trigger vagal syncope. In this study we examined the role of the peripheral venous compartment in the sequestration of blood as a cause of abnormal ventricular filling in 31 patients with unexplained syncope. Using a radionuclide blood pool label we measured the percentage change in venous volume on prolonged head up tilting and as an index of venous tone variability or responsiveness, the difference between maximum and minimum calf blood volumes (tilted) being expressed as a percentage of the mean volume. The patients were divided into two groups based on their response to tilt: those who developed syncope or near syncope (n = 6) and those who had no symptoms on tilting (n = 25). Patients with symptoms had a greater fall in systolic blood pressure (65·7 (10·1) *v* 14·2 (2·4) mm Hg, p < 0·001) and a greater increase in venous volume than those without symptoms (72% (7·4) *v* 52 0% (5·0), p = 0·05). However, venous tone variability was significantly less in the patients with symptoms (4·4% (0·9) *v* 14·1% (1·3), p = 0·001). The patients with symptoms were older but when compared with patients of a similar age they still had significantly less venous tone variability.

In conclusion, patients with the malignant vasovagal syndrome have an abnormal peripheral venous compartment that does not respond to a falling central pressure, which may cause the progressive sequestration of blood that culminates in vasovagal syncope.

Cardiovascular benefits of closure of arteriovenous fistulas in renal transplant recipients

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After successful renal transplantation arteriovenous fistulas previously used for haemodialysis are redundant but potentially lead to high output heart failure, thrombosis, and infection. The cardiovascular effects of routine closure of these fistulas have been inadequately explored. Seven patients (four male, three female; mean age 43 years) were studied immediately before and 3 days and 4 months after surgical closure of their arteriovenous fistulas (mean flow 1025 ml/min, range 575–1345). Exercise duration was assessed on Bruce protocol treadmill testing, left ventricular dimensions by echocardiography, and cardiac output by Doppler ultrasonography. Exercise duration increased by 11% at four months with respect to initial values (615 (185) s to 682 (194) s, p = 0·012). Maximum systolic blood pressure reached at peak exercise was 7% lower at four months than preclosure (197 (17) to 183 (18) mm Hg, p = 0·016) but the maximum rate-pressure product achieved was unchanged. Resting systolic pressure was lower at four months, having fallen markedly in the acute phase (142 (20) to 131 (19) to 140 (11) mm Hg). Recovery times were unaltered and there were no ischaemic symptoms or electrocardiographic changes with exercise. Stroke distance fell by 17% acutely (29·1 (5·4) to 24·2 (6·3) cm, p = 0·019) and remained 14% lower at four months (24·9 (5 5) cm). Cardiac output followed this trend (6·0 (2·0) to 5·3 (1·8) to 5·6 (1·9) l/min) but was maintained by a compensatory increase in resting heart rate (64 (12) to 70 (14) (p = 0·05) to 69 (20) beats/minute). Left ventricular end systolic dimensions fell by 10% immediately after closure and remained smaller at four months (2·63 (0·39) to 2·36 (0·38) to 2·62 (0·69) cm). Similarly, end diastolic dimensions fell by 9% acutely (4·46 (0·44) to 4·06 (0·42) to 4·38 (0·56) cm). Interventricular septal thickness was less at four months than before closure (18·0 (2·3) to 17·5 (3·5) mm). Drug treatment was constant during the study.

Closure of arteriovenous fistulas in renal transplant recipients whose condition is stable is associated with a number of beneficial cardiovascular benefits and should be routinely performed in transplant recipients.

Structure and cellular composition of aortic atherosclerotic plaques undergoing ulceration

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Plaque fissuring is a precursor of acute thrombosis in coronary arteries. The caps of aortic plaques undergo an identical process of tearing leading to ulceration but the time course is more prolonged. Aortic plaques undergoing ulceration were compared with intact plaques of equivalent size in the same aorta. The volume composition of the plaque for lipid and collagen was measured as well as the density of macrophages and smooth muscle cells after identification of the cells by double immunohistochemical staining. Smooth muscle cells were identified by the presence of α actin and macrophages by the presence of the HAM56 antigen. Aortic plaques undergoing ulceration ($n = 24$) when compared with intact plaques ($n = 62$) had a higher proportion by volume of extracellular lipid (54·9% (SEM 3·8) *v* 22·1% (2·4)). The mean macrophage density was increased (122·1 (13·3) *v* 62·2 (8·8)) and the mean smooth muscle count was decreased (65·2 (13·2) *v* 122·1 (13·3)) in ulcerated plaques compared with intact plaques. The ratio of smooth muscle cells to macrophages exceeded 5 in intact plaques but was often less than 1 in ulcerated plaques.

The two major factors predisposing to plaque ulceration are an increase in the volume of extracellular lipid and a decrease in the ratio of smooth muscle cells to monocytes in cap tissue.

Impact of thrombolytic treatment on morbidity and mortality from acute myocardial infarction in clinical practice

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Thrombolytic treatment reduces infarct mortality in patients selected for randomised trials but its impact on morbidity and mortality in clinical practice has not been clearly defined. We compared the outcome in 178 consecutive patients admitted to our coronary care unit (CCU) during 1990 with 158 consecutive controls admitted during 1986, before thrombolytic treatment was used in our unit. Only patients fulfilling World Health Organisation criteria for acute infarction were included. Data for 1990 were collected prospectively but, because retrospective controls were used, we were careful to analyse only those end points that could be identified unequivocally from a review of the patient records. Of the 178 admissions in 1990, 154 (87%) received thrombolytic treatment. This high treatment rate substantially improved morbidity and mortality compared with 1986, presumably because of reductions in infact size. Thus peak creatine kinase activity fell from 2022 (1312) to 1432 (1290) IU/l ($p < 0\cdot001$) and with it the incidence of cardiogenic shock from 20% to 6% ($p < 0\cdot001$). Indeed, reductions in all degrees of heart failure were observed, as reflected by take home prescriptions for diuretics, which fell from 42% to 22% in patients leaving hospital ($p < 0\cdot001$). There was also a significant reduction in the incidence of ventricular fibrillation from 22% to 13% ($p < 0\cdot05$). Hospital mortality in 1986 was 24% but in 1990 fell to 11% ($p < 0\cdot005$). It is noteworthy that patients who did not receive thrombolytic treatment in 1990 were a very high risk group with a mortality of 28% compared with 9% in the treated group ($p < 0\cdot01$). Improvements in morbidity and mortality led to reductions in the length of stay in the CCU from 3·1 (2·1) to 2·0 (1·4) days ($p < 0\cdot001$).

In conclusion, thrombolytic treatment has substantially reduced hospital mortality in acute myocardial infarction, though not necessarily to the very low levels reported in some clinical trials. It has also had a profound effect on the incidence of major complications, particularly cardiogenic shock and ventricular fibrillation. Additional benefits include reductions in the length of stay in the CCU and the need for long term diuretic treatment, both of which may have important resource implications.

Can thrombolytic treatment produce beneficial effects in the absence of coronary recanalisation during acute myocardial infarction?

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Evidence suggests that the beneficial effects of thrombolytic treatment cannot be explained by recanalisation of the occluded artery alone and that other factors may be involved. To investigate this we studied changes in haemodynamics, incidence of arrhythmias, and infarct size in anaesthetised rabbits undergoing coronary artery ligation (CAO) with and without intravenous streptokinase (15 000 U/kg administered 2 minutes after ligation). Reperfusion was initiated by removal of the ligature and infarct size was measured by planimetry of nitro blue tetrazolium stained left ventricular transverse sections (3 mm thick). Hearts were studied in four groups: group I ($n = 12$) control hearts with CAO for 60 minutes and no reperfusion; group II ($n = 12$) undergoing CAO for 60 minutes with streptokinase but no reperfusion; group III ($n = 12$) undergoing 30 minutes CAO and 30 minutes reperfusion induced by removal of the ligature; group IV ($n = 12$) undergoing 30 minutes CAO with steptokinase and 30 minutes reperfusion. Treatment with streptokinase had no significant effect on haemodynamic changes or the incidence of arrhythmias between the groups. Streptokinase did, however, reduce total left ventricular infarct size in the non-reperfused and reperfused groups: 35% (group II, non-reperfused) *v* 45% (group I, non-reperfused controls) ($p < 0\cdot001$), and 15% (group IV, streptokinase and reperfusion) *v* 25% (group III, reperfused controls) ($p < 0\cdot01$).

These results show that streptokinase inhibits the early development of necrosis in the presence of a persistent coronary artery occlusion.

Prediction of coronary patency: abrupt electrocardiographic changes versus ventricular late potentials

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The two aims of this study were (*a*) to compare ventricular late potentials (VLP) and abrupt changes on 12 lead electrocardiograms in predicting patency after thrombolysis (group 1) and (*b*) to predict patency by using VLP in the convalescent period in a group of patients not treated with thrombolysis (group 2). Coronary angiography was performed in 79 patients in group 1 and 36 in group 2. Of the

45 patients in group 1 with abrupt electrocardiographic changes, 42 (93·3%) had patent infarct related arteries. Of the 34 who did not have these changes, 15 (44·1%) had occluded vessels. Abrupt electrocardiographic changes predicted an open artery with a specificity of 83·3% and a sensitivity of 68·9%. Of the same 79 patients, 14 had VLP. Twelve (85·7%) had occluded vessels. Of the 65 who did not have VLP, 59 (90·7%) had open arteries. The absence of VLP predicted patency with a higher sensitivity (96·1%) but lower specificity (66·7%). Of the 19 patients without abrupt electrocardiographic changes and open arteries, 17 (89·5%) did not have VLP. Almost all of this group would be correctly identified by the absence of VLP. Of the 36 patients in group 2, all 13 with VLP had occluded vessels. Of the 23 who did not have VLP, 18 (78·3%) had open arteries. The absence of VLP predicted an open artery with a sensitivity of 100% and a specificity of 72·2%. Multivariate analysis identified VLP as a more powerful predictor of patency ($p < 0{\cdot}0001$) than abrupt electrocardiographic changes ($p = 0{\cdot}016$).

In conclusion, the absence of VLP is a more accurate, non-invasive means of predicting patency and may be useful in identifying which patients have patent arteries and would benefit from further invasive investigations.

Dynamic changes in QT dispersion during the early phase of acute myocardial infarction: relevance for ventricular fibrillation

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Dispersion of repolarisation is widely regarded as critical in producing ventricular fibrillation after myocardial infarction yet it has been inadequately studied during the acute phase in humans. In patients taking class III antiarrhythmic drugs we have shown increased QT dispersion in those manifesting proarrhythmic effects. Increased QT dispersion is also a feature of the long QT syndrome, in which abnormalities of repolarisation are the basis of the associated ventricular arrhythmias. We studied the changes in QT dispersion in the early phase of myocardial infarction with patients with unstable angina as a control population. We studied prospectively 33 patients admitted with chest pain by using 12 lead electrocardiograms at 50 mm/s and a digitiser based computer program. Patients with QRS prolongation or arrhythmias or taking antiarrhythmic drugs were excluded. QT dispersion was defined as QT maximum – QT minimum, values being rate corrected. Sixteen patients had acute myocardial infarction (eight anterior, eight inferior), the mean time from onset of symptoms to admission being five hours. Thirteen patients had unstable angina and four were excluded (two because of cardiomyopathy, two because of inadequate electrocardiographic data). There was no difference in QT dispersion between patients with anterior and inferior infarcts. QT dispersion was significantly greater in the patients with acute infarction (mean 86 (30) ms) compared with those with unstable angina (33 (14) ms) ($p < 0{\cdot}001$). QT maximum was prolonged in those with infarction (430 (33) ms) compared with those with unstable angina (390 (27) ms) ($p < 0{\cdot}001$) whereas QT minimum was unchanged (355 (31) *v* 357 (28) ms). In 12 patients with acute infarction a further electrocardiogram was recorded within 24 hours (mean 14). QT dispersion diminished in 11 out of 12 patients and was unchanged in one (mean reduction 35 (31) ms) $p < 0{\cdot}01$. Two patients with infarcts suffered ventricular fibrillation within two hours of admission, having QT dispersions of 90 and 130 ms.

Dynamic changes in QT dispersion occur after acute myocardial infarction and may reflect the electrophysiological conditions favouring early ventricular fibrillation.

Prediction of sudden death in first year after myocardial infarction from autonomic tests: influence of age

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To refine postinfarction risk stratification we examined the influence of age on the prediction of sudden death after infarction from autonomic tests. Of 481 patients followed up for a mean of 790 days after acute myocardial infarction, 60 (12·4%) died. Of the 269 young patients (aged <60 years), 22 (8·2%) died; 12 (54·6%) of these deaths were sudden. Of the 212 older patients (aged ≥ 60 years), 38 died (18%); eight (21%) of these deaths were sudden. The following relations were found between a heart rate variability index of < 160 ms of the baseline width of the histogram of RR interval durations, exercise duration of <3 minutes (EX3), ventricular ectopic frequency > 10 beats per hour (VE10) and sudden death in the two age groups. Heart rate variability index had a sensitivity of 92%, a specificity of 67·8%, a positive predictive accuracy of 11·7%, and a risk ratio of 21·0 in young patients ($p < 0{\cdot}001$) but a sensitivity of 62 5%, specificity of 60·4%, positive predictive accuracy of 6 5%, and a risk ratio of only 2·4 in older patients (NS). The combination of heart rate variability index with EX3 or VE10 in young patients had a sensitivity of 83%, a specificity of 90%, a positive predictive accuracy of 27%, and a risk ratio of 31 4 ($p < 0\ 001$) but in older patients had a sensitivity of 50%, a specificity of 73·6%, a positive predictive accuracy of 6·7%, and a risk ratio of only 2·6 (NS).

Sudden death accounts for a higher proportion of deaths and is more reliably predicted by autonomic tests in younger rather than older patients. Autonomic tests did not predict sudden death in older patients.

Embolisation of atrioventricular node with microvascular collagen: new treatment for atrioventricular nodal tachycardia

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Modification of the atrioventricular node by direct current or radiofrequency energy has recently been described for the treatment of atrioventricular nodal re-entry tachycardia without the need for permanent pacing. A transcoronary approach for nodal ablation has been another new development. We investigated the feasibility of transcoronary modification of the atrioventricular node by embolisation with microvascular collagen with the aim of producing limited nodal and perinodal damage. Three patients with highly symptomatic drug refractory atrioventricular nodal re-entry tachycardia underwent selective catheterisation of the atrioventricular nodal artery with a 2·2F infusion catheter. Microfibrillar collagen 2 mg/ml (Target therapeutics ANGIOSTAT) was injected over 2 seconds (0·1 ml in case 3 and 0·5 ml in cases 1 and 2). All patients developed transient complete atrioventricular block. One patient (case 3) still had symptoms and subsequently underwent electrical modification. At restudy after eight weeks the two other patients were free of inducible tachycardia and had no evidence of dual atrioventricular nodal pathways. The mean AH interval increased from 65 ms to 72 ms, atrioventricular nodal effective refractory period from 290 ms to 310 ms, and atrioventricular nodal Wenckebach cycle length from 240 ms to 350 ms (cases 1 and 2). There were no changes in any of these parameters in the remaining patient, the failure of the procedure probably being explained by the low dose of collagen used. As the natural history of such lesions is unknown, permanent pacemakers were inserted in all patients. This technique may result in ablation of the slow conducting pathway without appreciably altering the properties of the fast pathway.

Embolisation of the atrioventricular node with microvascular collagen is a new and potentially valuable technique for modification of atrioventricular nodal function in patients with atrioventricular nodal re-entry tachycardia.

Successful catheter ablation of substrate for atrial flutter with multiple direct current shocks

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Atrial flutter in humans is due to a macro re-entry circuit in the right atrium with an area of slow conduction posteroinferiorly near the os of the coronary sinus. We ablated this area of slow conduction in seven patients (seven men aged 50–67) with refractory atrial flutter by using low energy direct current shocks. This was achieved in four patients—three in established atrial flutter (mean duration 17 months)—during attempted His bundle ablation. The ablation catheter was positioned to give a large atrial signal with a minimal His deflection and 3–10 shocks were delivered (cumulative energy 75–200 J) Although complete atrioventricular block was achieved in three patients initially, conduction had returned by one month. However, all four patients remained in sinus rhythm and free of arrhythmia during follow up (8–15 months). We have now prospectively attempted selective ablation of the atrial flutter substrate in three further patients with refractory atrial flutter. Twelve to 15 low energy shocks (cumulative energy 105–235 J) were delivered directly to the atrial wall at multiple sites in the triangle of Koch. At early follow up (3-5 months) two patients remained free of atrial flutter, though one developed previously undocumented atrial fibrillation.

Successful catheter ablation of atrial flutter can be achieved by multiple low energy direct current shocks.

Electrophysiological effects of pharmacological load manipulation by converting enzyme inhibitors and vasodilators in patients with impaired left ventricular function

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There is growing interest in the contribution of contraction-excitation feedback to the pathogenesis of ventricular arrhythmias in failing hearts. The electrophysiological effects of pharmacological load manipulation by captopril and a combination of hydralazine with oral nitrate were investigated in eight patients with left ventricular dysfunction (ejection fraction 22% (8)) and recurrent ventricular tachycardia inducible by programmed electrical stimulation. Subjects were tested (not taking antiarrhythmic drugs) on three treatment regimens in random order: captopril, hydralazine-nitrate, and control (no vasodilator). Captopril and hydralazine-nitrate were dose titrated to reduce systolic pressure by 10–20%. Programmed electrical stimulation was performed according to a 12 step protocol (maximum three extrastimuli). Repolarisation was assessed from monophasic action potential duration (mean of 4–6 sites) and QT interval during atrial pacing at a cycle length of 500 ms. Compared with control, hydralazine-nitrate and captopril produced similar falls in peak systolic pressure (19% (10) and 15% (9)), although hydralazine-nitrate caused a bigger reduction in systemic vascular resistance (39% (22) *v* 24% (17)) and pulmonary capillary wedge pressure (12 (5) *v* 6 (3) mm Hg). Hydralazine-nitrate produced no significant change in refractoriness or repolarisation compared with control. By contrast, captopril increased ventricular effective refractory period from 231 (26) to 249 (23) ms ($p < 0·02$) and functional refractory period from 255 (24) to 267 (27) ms ($p < 0·05$). There was also prolongation of the QT interval from 351 (28) to 358 (25) ms ($p < 0·05$), but no corresponding change in monophasic action potential duration was seen. Inducibility of ventricular tachycardia by programmed electrical stimulation did not differ significantly with any regimen.

We conclude that the prolongation of ventricular repolarisation and refractoriness by captopril cannot be explained solely on the basis of altered ventricular loading, given the lack of change with hydralazine-nitrate. Specific autonomic and cell membrane effects of converting enzyme inhibitors may also be involved.

Temperature controlled radiofrequency atrioventricular nodal ablation

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Problems with conventional high energy atrioventricular nodal ablation have led to a search for alternative means of performing this procedure. Radiofrequency energy is one of these alternatives which has many advantages over conventional techniques, such as less discomfort and less myocardial damage. However, its major drawback is the difficulty in controlling catheter tip temperature, which can lead to tissue charring. We evaluated a new temperature controlled radiofrequency ablation system in nine patients (aged 26–59 years). The condition of all of them was refractory to previous drug treatment. Arrhythmias comprised paroxysmal atrial fibrillation (three), paroxysmal atrial tachycardia (one), intranodal re-entry tachycardia (five). All had a satisfactory symptomatic result. In the four patients with atrial arrhythmias we obtained complete heart block (three) or high grade block (one) and performed pacemaker implantation. Selective partial ablation was achieved in four of the five patients with accessory nodal pathways. Sinus rhythm was maintained and no additional treatment was necessary. In one of these patients complete heart block was produced necessitating permanent pacing. In one patient there was a recurrence of nodal re-entry at six weeks but at a slower rate than before and now easily controlled by propafenone.

This new ablation technique seems to be successful in providing both complete and selective partial nodal ablation without significant discomfort (no patient required general anaesthesia) or subsequent complications (follow up 2–6 months).

Surgical management of atrioventricular nodal re-entrant tachycardia

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Surgical treatment of atrioventricular nodal re-entrant tachycardia (AVNRT) was first described in 1985. Since 1987 we have operated on 11 patients (mean age 39 years, range 21–64; eight women) with AVNRT and documented duel atrioventricular nodal pathways. Three patients also had accessory atrioventricular connections (two left free wall, one left posteroseptal), which were dealt with by endocardial dissection at the time of operation, and one had a coexisting atrial tachycardia. Patients had been treated with a mean of five antiarrhythmic agents; one patient had previous electrical atrioventricular nodal modification and another had had an antitachycardia pacemaker fitted. The first two patients underwent surgical dissection of the atrioventricular node and the succeeding patients had cryosurgical lesions of 3 mm in diameter produced by freezing for two minutes at −60°C. These lesions were placed around the atrioventricular node and between the node and coronary sinus os during atrial pacing. If the atrioventricular interval increased by more than 100 ms or if any higher degree of atrioventricular block occurred the cryotherapy was immediately discontinued and the area irrigated with warm saline. The mean bypass time was 102 minutes. Postoperatively one patient developed a left haemothorax requiring drainage and two patients developed chest infections. Electrophysiological studies were performed at one week; no patient had inducible tachycardia and four had no retrograde conduction. During a mean follow up of 12 months (range 1–40) 10 out of 11 (91%) patients were free of AVNRT. Two patients developed atrial flutter and one paroxysmal atrial fibrillation and one patient underwent a His bundle ablation for atrial tachycardia. Complete atrioventricular block was produced at the time of operation in one patient and second degree atrioventricular block in one patient, both of whom were paced.

In conclusion, surgical treatment of AVNRT offers a high success rate and should be recommended for suitable patients.

Low energy ablation of ventricular tachycardia

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The report of the world registry for catheter ablation concludes that catheter ablation remains a treatment of last resort for ventricular arrhythmias because of poor efficacy (18%), a procedure mortality of 7%, and mortality at one month of 24%. We describe our experience with a low energy system in 11 consecutive patients with drug refractory ventricular tachycardia (VT) or poor tolerance of drugs. The mean age of these patients was 46 (range 23–75). Nine were men and two women. Four had arrhythmogenic right ventricular dysplasia, one had a normal heart with right ventricular outflow tract tachycardia (RVOT), one corrected tetralogy of Fallot, three ischaemic heart disease (IHD), one xenograft aortic valve replacement (AVR), and one fascicular tachycardia (FT). Endocardial activation mapping and pace mapping localised earliest activation to the left ventricle in six and to the right ventricle in five. In three (two with arrhythmogenic right ventricular dysplasia, one with ischaemic heart disease) a suitable site was not found and no shocks were delivered. Two to 23 (mean 11) shocks of 3–30 J were delivered to the remaining eight patients (in one patient over two sessions). The range of cumulative energy delivered was 16–411 J (mean 220 J). There were no acute deaths or serious side effects. At follow up of 4–18 months (mean 11) three patients (RVOT, tetralogy of Fallot, fascicular tachycardia) had successful ablation of VT and were symptom free and not taking drugs. Ablation was unsuccessful in two (ischaemic heart disease, AVR). Modification was produced in three; two patients (ischaemic heart disease, arrhythmogenic right ventricular dysplasia) had no VT with a previously ineffective drug treatment and in one VT (arrhythmogenic right ventricular dysplasia) was eradicated for three months until a new configuration VT appeared.

This study shows that low energy catheter ablation of VT is a safe technique and that in 45% of patients permitted control of VT. Success (including modification) is higher (80%) for ventricular tachycardias arising from the right ventricle than for that arising from the left (33%). This may be due to a more localised substrate in the right ventricle and more difficult catheter manipulation in the left ventricle.

Intimal proliferation in organ culture of human internal mammary artery

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Arterial intimal proliferation is an early feature of atherosclerosis. However, its progression in humans is difficult to study. We therefore attempted to develop an organ culture model of intimal proliferation using segments of human internal mammary artery (IMA). Segments of IMA were dissected free from adventitia, carefully opened out, and cultured intimal surface uppermost for 14 days at 37°C in RPMI 1640 containing 30% fetal calf serum. In a separate experiment segments of IMA had the endothelium removed before culture. Tissue viability was assessed by ATP to ADP ratio, endothelial coverage by scanning electron microscopy, and immunostaining for von Willebrand factor antigen and cell proliferation by autoradiography of histological sections. The ATP to ADP ratio of IMA did not significantly alter after 14 days in culture (1·6 (SEM

0·2) *v* 2 0 (0·2) (n = 10)), indicating that tissue viability was maintained. Intimal proliferation was observed in histological sections of cultured IMA. Immunostaining revealed that these neointimal cells were weakly positive for α actin, suggesting a differentiation towards a type of smooth muscle cell. Autoradiography showed proliferating cells in the neointimal layer with few dividing cells in the medium. De-endothelialised IMA showed less neointimal thickening when compared with intact IMA (21 (2) μm *v* 36 (7) μm) (n = 6, p < 0 05) as well as a reduced number of dividing cells per millimetre intimal length (4·1 (0·6) per mm *v* 6 7 (1·3) per mm) (n = 6).

Thus, an organ culture model of human arterial intimal proliferation has been established. De-endothelialisation results in diminished neointimal thickening, providing evidence for an endothelial derived proliferation enhancing factor. Inhibitors of this factor may therefore present new possibilities for treatment.

Activation of endothelial monocyte adhesion associated with intimal proliferation in organ cultures of human saphenous vein

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Endothelial activation may be a common factor mediating atherogenesis in coronary arteries and vein grafts. Intimal smooth muscle cell proliferation, which is a characteristic feature of atherogenesis, occurs in an endothelium dependent manner in organ cultures of human saphenous vein. We investigated whether increased leucocyte adhesion, a marker for endothelial activation, also occurred in these cultures. Saphenous vein obtained from patients undergoing a coronary artery bypass operation was opened out and 6 mm diameter discs were cut with the blade of a corneal trephine. Discs were cultured for 14 days in RPMI medium containing 30% (v/v) fetal bovine serum, supplemented for the last 24 hours with 1 μCi/ml of tritiated thymidine. Intimal proliferation was quantified from autoradiographs of 5 μm transverse paraffin sections. Adhesion of 2×10^5 monocytes labelled with chromium-51 was measured by incubation for two hours at 37°C, followed by washing 20 times at a medium-air interface, and was further defined by scanning electron microscopy. Culture of discs (n = 9) led to the development of a neointima 24 (7) μm thick, which contained 15·4 (2·1) thymidine labelled cells per mm of section length. The proportion of monocytes adhering to freshly isolated vein (7·1% (1·2), n = 8) was not affected by culturing (6·4% (0·8), n = 8), but the distribution of adhering cells was altered. Monocytes adhered preferentially to endothelium denuded areas of freshly isolated vein whereas in cultured veins, where there were no endothelium denuded areas, monocytes adhered preferentially to cells with typical endothelial morphology. Adhesion of monocytes to endothelium was confirmed in transverse sections specifically stained with *U europaeus* lectin.

Thus, monocytes adhered readily to the endothelial cells of cultured but not freshly isolated saphenous vein. This indicates that the endothelial cells responsible for stimulation of intimal smooth muscle cell proliferation are indeed activated.

17β-Oestradiol induces endothelium independent vasodilatation in isolated sheep coronary arteries

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Treatment with oestrogen reduces the risk of coronary heart disease in postmenopausal women. Protection against transient myocardial ischaemia and infarction by modulating coronary artery tone could be an important mechanism. This study assessed the relaxing effect of 17β-oestradiol on isolated sheep coronary arteries and the role of endothelium in this relaxation. Left anterior descending coronary arteries from adult male sheep were dissected free of fat and connective tissue. The endothelium was removed from alternate rings by gently rubbing the tissue with a wooden probe. Each ring (2–3 mm in length) was suspended in an organ bath containing modified Krebs solution at 37°C, bubbled with 95% oxygen and 5% carbon dioxide. Rings were allowed to stabilise for 90 minutes under a basal tension of 1 g. 17β-Oestradiol (0 1, 1, 10 μM dissolved in ethanol) or the same concentration of ethanol was added to the bath eight minutes after rings were precontracted with potassium (30 mM), which induced comparable contractile responses in rings with and without endothelium (1·8 (0·7) and 1·7 (0·9) g respectively, n = 6; unpaired *t* test, p > 0·05). 0·1 μM 17β-Oestradiol had no effect on precontracted rings (p > 0·05). 1 and 10 μM 17β-oestradiol induced significant relaxation by 33% (2) and 84% (4) in precontracted rings with endothelium and 33% (3) and 79% (6) in rings without endothelium (comparison with ethanol controls, n = 6, p < 0·01). No differences were seen between rings with and without endothelium (p > 0·05). Furthermore, reduced haemoglobin (10 μM), an inhibitor of endothelium derived relaxing factor dependent vasodilatation, and indomethacin (10 μM), an inhibitor of prostacyclin dependent vasodilatation, did not affect 17β-oestradiol induced relaxation.

Thus, our results indicate that 17β-oestradiol induced significant relaxation in precontracted sheep coronary arteries by an endothelium independent mechanism. These results may help to explain the beneficial effect of oestrogen replacement therapy in postmenopausal women.

17β-Oestradiol inhibits calcium currents in isolated single guinea pig cardiac myocytes

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The negative inotropic effect of 17β-oestradiol on the myocardium from perfused rabbit heart has been described previously but the underlying mechanism is not understood. The purpose of this study was to assess the possible inhibitory effect of 17β-oestradiol on the inward calcium current in isolated single cardiac myocytes. Guinea pig ventricular myocytes isolated by enzymic perfusion were continually superfused with a modified Krebs solution containing 2·5 mM calcium bubbled with 95% oxygen and 5% carbon dioxide at 22°C. Microelectrodes were filled with either 3 M potassium chloride or 2·1 M potassium citrate and 60 mM potassium chloride and had resistances of 15–25 $M\Omega$. 17β-Oestradiol caused action potential duration to decrease in a dose dependent manner. Action potential duration decreased to 82·1% (1·6) in 3 μM 17β-oestradiol and to 74·3% (8·1) in 30 μM 17β-oestradiol (n = 6, mean (SD)) within 1–3 minutes. 17β-Oestradiol also caused shape changes in the early part of the action potential, notably a more depolarised early plateau consistent with an inhibition of the calcium current. We used an Axoclamp 2–A in switch clamp mode to measure the calcium current. Cells were voltage clamped, held at −40 mV, and subjected to step depolarisations from this voltage to elicit the calcium current. This current could be blocked by verapamil, cobalt, and cadmium and increased by isoprenaline or by increasing the external calcium concentration. After one minutes' perfusion 10 μM 17β-oestradiol decreased the calcium current by 45% (7) without significant alteration to the shape of the current-voltage relation. The effect of 17β-oestradiol was reversible after washout for two minutes. The reversible inhibition indicated that the effect of 17β-oestradiol could not be due to run down of the calcium current.

Our results suggest that 17β-oestradiol inhibits inward calcium current and this may underlie its negative inotropic effect.

Heat stress protects isolated perfused rabbit heart

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Developing means of protecting the ischaemic myocardium has been the goal of cardiologists for many years. It is now realised that other than the early restoration of coronary blood flow, which is itself associated with reperfusion induced injury, little can be done by drug treatment to salvage muscle and limit the ultimate size of an evolving infarct. We investigated a new approach to protect the ischaemic and reperfused myocardium. Hyperthermia is known to induce the synthesis in the heart of a small group of proteins known as the heat shock or stress proteins, which may be able to protect the heart from a further stress. We confirmed initial protective findings associated with heat stress in rat hearts and extended this work to another species—namely, the rabbit. Rabbits (n = 8) were anaesthetised and body temperature raised to 42°C for 15 minutes (heat shock). Controls (n = 8) were treated in the same way but without heating. After 24 hours the animals were reanaesthetised and the hearts removed for heat shock protein analysis (n = 6) or perfusion with Krebs buffer. Hearts were subjected to 60 minutes of low flow (1 ml/minute) ischaemia followed by 30 minutes of reperfusion and evaluated for recovery of function, creatine kinase release, tissue ATP and creatine phosphate concentrations, mitochondrial function, and glutathione release. On reperfusion hearts subjected to heat shock showed improvements in diastolic pressure (37·1 *v* 53 7 mm Hg), post-reperfusion developed pressure (30 *v* 18 mm Hg), creatine kinase release (560 *v* 1105 mU/min/g), glutathione release (0·003 *v* 0·4 nmoles/min/g), and concentrations of ATP (6·1 *v* 2·8 μmol/g) and creatine phosphate (36·9 *v* 17·4 μmol/g). In addition, the mitochondrial respiratory control index was higher in the heat shocked animals (9·2 *v* 5 7). Western blotting showed raised 72 kilodaltons heat shock protein in the heat shocked hearts compared with controls.

These data extend the hypothesis that heat shock protects against ischaemia and reperfusion in this model. This raises the possibility of exploiting intrinsic cellular mechanisms to protect the heart from ischaemic and reperfusion damage.

Intercellular adhesion molecule-1 expression on cardiac vascular endothelial cells in dilated cardiomyopathy

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The hyperexpression of intercellular adhesion molecule-1 (ICAM-1) and class II major histocompatibility complex antigens on vascular endothelial cells occurs in organs affected by chronic inflammation or autoimmunity, or both. ICAM-1 and class II expression on cardiac vascular endothelial cells was studied in fresh biopsy tissue from 29 patients with dilated cardiomyopathy (20 men, nine women, mean age 45 (11) years) and in surgical specimens from 40 control patients (28 men, 12 women, mean age 44 (18) years), of whom nine had congenital defects, 20 coronary artery disease, and 11 longstanding rheumatic heart disease. Double immunofluorescence was performed with monoclonal antibodies to ICAM-1 or to class II and with antiserum to human factor VIII as a vascular endothelial cell marker. Class II expression on vascular endothelial cells was more frequent in patients with dilated cardiomyopathy than in controls (27/29 (93%) *v* 11/40 (27·5%), p = 0·0001). The finding of ICAM-1 expression on vascular endothelial cells was also more common in patients with dilated cardiomyopathy than in controls (13/29 (45%) *v* 5/40 (12·5%), p = 0·006). A positive association was found between ICAM-1 and class II antigen expression; ICAM-1 expression was more commonly found in class II positive tissues than in class II negative specimens (16/38 (42%) *v* 2/31 (6%), p = 0·002). Sensitivity, specificity, and predictive value of class II and of ICAM-1 molecule expression as tissue markers of dilated cardiomyopathy were 93%, 72%, 67% and 45%, 87%, 38% respectively.

In dilated cardiomyopathy expression of class II major histocompatibility complex antigens on vascular endothelial cells is a sensitive and relatively specific marker of autoimmunity while the finding of ICAM-1 induction on cardiac vascular endothelial cells may represent a secondary response to chronic inflammation.

Frequency response characteristics of intraventricular balloons used for functional assessment of isolated hearts

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Fluid filled intraventricular balloons have been used experimentally for many years to measure the function of isolated perfused hearts. To assess their accuracy balloons were placed in a pressure chamber containing a high quality pressure transducer (response flat to 100 Hz) and a pressure wave generated over a frequency range of 0–60 Hz. Frequency response curves were then constructed by comparing the response of both monitoring systems with differing arrangements of balloons, tubing, and transducers to assess the contribution of each component in the system. Balloons were constructed of stretched plastic foil (about 600 μl in volume), and after filling with water and air evacuation they were attached by means of polythene tubing (100 cm long, 1 mm internal diameter) to a pressure transducer. Frequency response curves were generated at different balloon volumes (30, 70, 100, 130 μl). The frequency response curves of individual balloons were almost superimposable at all balloon volumes, but there were significant differences between the curves of each balloon ($p < 0{\cdot}05$ at 20 Hz). The pattern of response was of amplification of the signal (> 3 dB) between 12·6 (3 2) Hz, up to a maximum of 9·0 (0·8) dB, and then of progressive signal attenuation (-3 dB cut off 48 5 (9 5) Hz). Changing the pressure transducer did not significantly alter the frequency response curve of each balloon. Removal of the polythene tubing from the system resulted in significantly greater resonance between 30 and 60 Hz ($p < 0$ 01). The results indicated that cardiac measurements of systolic and developed pressure (component frequency range 0–25 Hz) would be mildly amplified but measurements of dP/dt, which focus specifically on the high frequency signals, would be severely distorted.

We conclude that, firstly, intraventricular balloons show both resonance (12–25 Hz) and filtering which distorts pressure measurements. Secondly, the frequency response curve of every balloon should ideally be characterised before use. Thirdly, analysis of dP/dt is likely to be inaccurate and unreliable. Finally, the limitations of balloon measurements should be appreciated.

Decision making regarding thrombolytic treatment in the community: is the ECG useful?

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We assessed the roles of clinical assessment and electrocardiography performed at home in decision making for thrombolytic treatment outside hospital. A total of 137 patients seen at home with chest pain requiring direct admission to the coronary care unit (CCU) were assessed prospectively on clinical grounds by their general practitioner (GP), who documented suitability for the administration of thrombolytic treatment. Patients were randomised to clinical assessment only (group 1) or clinical assessment followed by a further assessment after electrocardiography (group 2). An electrocardiogram was successfully completed for 55 patients (76%), of which 11 were of poor quality. The decisions were compared with the prescription of thrombolytic treatment in the CCU. In group 1 thrombolytic treatment was recommended in 30 out of 82 patients, of whom 10 ultimately received thrombolytic treatment (predictive value 33%), and not recommended in 52, of whom three received thrombolytic treatment (predictive value 94%). In group 2 after clinical assessment alone thrombolytic treatment was recommended in 19 out of 55 patients and given to eight (predictive value 42%) and was not recommended in 36, of whom five received thrombolytic treatment (predictive value 86%). The clinical assessment was reversed after electrocardiography in seven patients, incorrectly in five.

Clinical assessment alone is unreliable for the prescription of thrombolytic treatment and difficulty exists in both recording and interpreting electrocardiograms at home, thus diminishing their contribution to decision making. Means of facilitating electrocardiogram recording and interpretation are required before thrombolytic treatment can safely be administered in the community.

Dundee coronary risk disk: an aid to preventive cardiology

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Coronary risk factor assessment is increasingly popular as an aid to coronary heart disease prevention. However, clinicians traditionally consider risk factors in one dimensional terms, in which low or average levels are acceptable, and action is taken if a certain level is exceeded. This has been the approach to blood pressure control and now forms the basis of cholesterol management algorithms. However, risk factors interact and clinicians are also encouraged to "take account of other risk factors" but cannot do so without a scoring system to make this possible. In collaboration with a joint committee of the Coronary Prevention Group and the British Heart Foundation a scoring system was developed incorporating smoking, blood pressure, and cholesterol concentration. A mechanical analogue, the Dundee coronary risk disk, has been produced. Its scientific basis and the results of evaluation by doctors and nurses are described, as well as its validation against the Whitehall study. It is suggested that it may not only be the yardstick for a high risk strategy in general practice but also help hospital doctors, particularly cardiologists, to assess and explain coronary risk factors.

Evidence of autonomic imbalance from analysis of heart rate variability in patients with and without exercise induced ventricular tachycardia in clinically normal hearts

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Spectral and non-spectral analysis of heart rate variability allows a non-invasive method of assessment of sympathetic and parasympathetic influences on the heart. Many patients with ventricular tachycardia (VT) in "clinically normal" hearts have exercise induced VT, suggesting a sensitivity to the changes in myocardial autonomic tone associated with exercise. We studied components of HRV in 19 patients (age range 19–60 years) with and without exercise induced VT and clinically normal hearts. 24 Hour Holter tapes obtained from patients receiving no treatment were analysed with a Marquette 8500 laser Holter system. Power spectral analysis of HRV showed that the low frequency (LF) components (0 05–1·5 Hz, representing parasympathetic elements) and high frequency (HF) components (0·15–0 4 Hz, representing sympathetic elements) or their ratio did not differ between patients with (low frequency 32·5 (11·8), high frequency 18·1 (11·3)) and without (low frequency 27·0 (11·7), high frequency 12·9 (7·0)) exercise induced VT. Non-spectral measures of heart rate variability included the SD of normal RR intervals, root mean square successive difference (rMSSD), and the percentage of RR intervals exceeding the preceding interval by 50 ms (pNN50). Although the SD of normal RR intervals did not differ in patients with and without exercise induced VT (136·8 (52·6) *v* 121·1 (34·9) ms), the rMSSD (38·7 (14·6) *v* 26·3 (10·3) ($p = 0·07$)) and pNN50 (15·5 (10·8) *v* 6·1 (6·4) ($p < 0·05$)) were higher in patients with exercise induced VT. The indices rMSSD and pNN50 are sensitive measures of parasympathetic activity and the results suggest a predominance of parasympathetic tone in patients with exercise induced VT.

We conclude that these data provide evidence of sympathetic-parasympathetic imbalance over short time periods in patients with exercise induced VT in clinically normal hearts.

QT interval dispersion and arrhythmic events in patients with congenital long QT syndromes: effects of β blockade

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Recent evidence has suggested that QT dispersion, recorded in a surface electrocardiogram, may be a predictor of the risk of arrhythmic events in patients with long QT interval syndromes (LQTS). We studied seven patients with congenital LQTS (six female, mean age 21 years, range 1 month–44 years), all of whom had documented torsade de pointes. All patients were studied while not receiving treatment and after a mean period of 38 months (range 2–116 months) of β blockade. Good quality electrocardiograms were recorded in all patients at a paper speed of 50 mm/s. The QT and RR intervals were measured in all leads; the QT_C interval for each lead and the dispersion between the minimum and maximum QT and QT_C intervals were calculated. The mean QT dispersion with no treatment was 109 (47) ms (QT_C 0·107 (0·031) $s^{\frac{1}{2}}$). With β blocking drugs the QT dispersion was 169 (60) ms (QT_C 0·158 (0·052) $s^{\frac{1}{2}}$). The QT and QT_C dispersion before and during β blockade was not significantly different. Seven of the eight patients had no further symptoms or documented arrhythmic events with β blockade. The one patient who continued to experience torsade de pointes with β blockade showed no difference in QT interval dispersion (115 *v* 115 ms) and a slight decrease in QT_C dispersion (0·127 *v* 0·093 $s^{\frac{1}{2}}$).

We conclude that patients with congenital LQTS have marked dispersion of the QT interval in a surface electrocardiogram. However, the beneficial antiarrhythmic effect of β blockade in these patients is not reflected in a lessening of this abnormal dispersion.

Diagnosis and management of vasovagal syndrome

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Between 1980 and 1990, 55 patients (29 women, aged 67 (14) years; 26 men, aged 59 (13) years) received pacemakers for treatment of the cardioinhibitory malignant vasovagal syndrome. The syndrome was diagnosed if there was clear documentation of vasovagal bradycardia or positive results in a tilt test (cardioinhibition to less than 60 beats/minute) but not if there was only a vasodepressor response to tilting. Symptoms were syncope (51 (93%) patients); presyncope (three (5%)); dizziness (one (2%)). Three patients died of unrelated causes and were excluded. The remaining 52 patients were followed up for a mean of 4·7 (2–126) months. Thirty two (62%) patients (group A) had complete abolition of symptoms with pacing; the condition of 16 (31%) (group B) was improved (four with additional drug treatment) and that of four (7%) (group C) was not improved. Tilt testing gave positive results in 43 (83%) patients, 25 (78%) in group A, 15 (94%) in group B, and three (75%) in group C. Resting or ambulatory electrocardiographic abnormalities (bradycardia, ischaemia) were identified in 21 (66%) patients in group A, 12 (75%) in group B, and three (75%) in group C. Electrophysiological study identified sinus node or atrioventricular conduction disease in 11 (34%) patients in group A, four (25%) in group B, and three (75%) in group C. Optimal pacemaker modes were: in group A DDI 27 (84%) patients (all with hysteresis and DDD five (16%) (two with hysteresis); in group B DDI 12 (75%) (10 with hysteresis), DDD two (13%) (one with hysteresis), and VVI two (13%) (one in atrial fibrillation); in group C DDI one (25%) (with hysteresis) and DDD three (75%).

Symptoms were abolished or considerably ameliorated by optimal cardiac pacing in 48 (92%) patients. DDI pacing was used in 40 (83%) of these (with hysteresis in 38 (95%)). Many had no demonstrable abnormality on electrophysiological study but most had positive results in a tilt test. Decision to pace, therefore, is not helped by the results of electrophysiological study but negative results in a tilt test do not preclude improvement by pacing if there is historical documentation of the cardioinhibitory malignant vasovagal syndrome.

Exaggeration of latency after premature stimulation in abnormal myocardium

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Conduction time is known to be prolonged (latency) after premature stimulation. To investigate the effect of myocardial disease on latency we delivered increasingly premature ventricular stimuli during steady state ventricular pacing (600 ms) at the right ventricular apex during electrophysiological study of patients without myocardial disease (controls) and patients with myocardial disease. Onset of activation at the right ventricular apex was determined by recording monophasic action potential (MAP) upstroke. Activation time at the right ventricular apex was measured as the interval from stimulus artefact to MAP upstroke. Activation time was consistently prolonged to a maximum with approach to refractoriness and was expressed as the percentage increase from steady state value ($\%AT_{max}$). In 10 controls mean $\%AT_{max}$ at 19 sites was 36·1% (SEM 6·4%). In seven patients with ischaemic heart disease and ventricular tachycardia $\%AT_{max}$ was

55·7% (11·1%) at 12 sites (no significant difference from controls). In nine patients with arrhythmogenic right ventricular dysplasia, however, %AT_{max} was 76·6% (13 3%), significantly greater ($p < 0·01$) than that in controls. In 12 patients with right and left ventricular disease (non-ischaemic) %AT_{max} was 81·9% (13·7%) at 24 sites, again significantly greater ($p < 0·01$) than that in controls. The mean %AT_{max} was also significantly greater than that in controls ($p < 0·01$) at 16 sites in seven patients receiving amiodarone for ventricular tachycardia complicating ischaemic heart disease (78·7% (10%)) and at 15 sites in four patients with arrhythmogenic right ventricular dysplasia receiving amiodarone (81·3% (11·9%); $p < 0·01$).

In conclusion, an exaggeration of the expected increase in latency with prematurity is a notable feature of myocardium with generalised disease. A consequence of this exaggerated increase in latency will be enhanced dispersion of repolarisation. Amiodarone may also exaggerate latency but this arrhythmogenic effect could be countered by prolongation of the action potential duration.

Transaortic ventricular tachycardia mapping during surgery

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Transannular left ventricular endocardial mapping during ventricular tachycardia surgery avoids a ventriculotomy but the problem remains of relating the map to anatomical structures and the precise delivery of an ablating system. We have developed a passive multijointed mechanical arm which terminates in a hand held probe that is inserted retrogradely through the aortic valve after the patient is placed on total cardiopulmonary bypass and the aorta has been incised and the coronary arteries have been cannulated and perfused. The movements of the six joints of the arm are sensed by a supervisory computer and the position of the electrode at the tip of the arm is calculated and displayed continuously on the computer monitor as a cursor over a stylised grid representing the left ventricular endocardial geometry. When electrograms are recorded their positions on the left ventricular endocardial surface are displayed on the map. The electrograms are processed to determine their activation sequences and the markers indicating their positions on the map are colour coded to display the activation pattern across the left ventricular endocardium. The points can also flash in the sequence of their activation, creating a dynamic display. The surgeon may then move the probe to any interesting point on the endocardium by aligning the cursor with the point on the map. Then the map can be refined interactively by sampling new positions that are less than 5 mm apart. The surgeon can, to some extent, identify the papillary muscles while exploring the left ventricular cavity and relate their positions to the positions of the electrograms recorded on the map. A case of non-ischaemic ventricular tachycardia originating in the left ventricular outflow tract, and hence inaccessible to a transmitral approach, has been mapped and successfully cryoablated with this method. We intend to extend this approach by building a cryoprobe into the tip of an exploring probe that can be attached to the arm in place of the mapping probe and placed precisely against the ventricular tachycardia focus.

Dietary fat enhances survival of rejecting cardiac allografts in rats

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Recent studies have suggested that polyunsaturated fatty acids, both ω-3 (N-3) and ω-6 (N-6), are immunosuppressive. This study tested the ability of Menhaden oil (MO), rich in ω-3 fatty acid, and safflower oil (SO), rich in ω-6 fatty acids, to prolong cardiac allograft survival. Lewis recipients and Lewis × Brown Norway donor rats were fed three test diets for six weeks. The beef tallow (BT) control diet and MO and SO diets were 20% by weight fat and varied only in fatty acid content. After six weeks Lewis recipients received an abdominal heterotopic transplant from the donor animals. Postoperatively half the animals were treated with cyclosporin at 5 mg/kg for the first 10 days; the remainder were untreated. Parameters measured were graft survival in days, animal growth, dietary fatty acid analysis, and dietary intake. Statistical analysis was by the Mann–Whitmey U test for non-parametric data. Animal growth and dietary intake were identical in the three dietary groups. The median graft survival and survival range were as follows: six BT grafts survived a median of 7 5 days (6–9), seven SO grafts 14·3 days (10–21), and 10 MO grafts 12·0 days (10–14). Six BT and cyclosporin grafts survived 18·0 days (17–19), six SO and cyclosporin grafts 34·5 days (26–76), and six MO and cyclosporin grafts 28·5 days (24–33). The test diets SO and MO were significantly different from the BT control diet with or without cyclosporin treatment ($p < 0·01$).

These data show that dietary polyunsaturated fatty acids prolong the life of rejecting cardiac allografts. It may be that such dietary fatty acids will reduce the dose of cyclosporin required for permanent allograft survival.

Right heart Doppler characteristics: comparative study of live (domino) and conventional donor hearts

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The recipient hearts from patients undergoing combined heart-lung transplantation (domino hearts) provide a valuable source of donor organs for cardiac transplantation. The right ventricle of these hearts is usually hypertrophied as an adaption to high pulmonary vascular resistance (PVR). It is conceivable that after engraftment, when these hearts are exposed to normal or near normal PVR, the now inappropriate hypertrophy may impair right heart filling. Accordingly, with Doppler echocardiography right sided filling was compared in 12 patients, of whom six (heart rate 87 (SD 13) beats/minute, age 50 (10) years; time since transplant 23 (13) months; ischaemic time 102 (34) minutes; donor age 29 (7) years) had received domino (D) hearts and six (heart rate 95 (17) beats/minute; age 53 (9) years; time since transplant 7 (7) months; ischaemic time 143 (52) minutes; donor age 31 (10) years) conventional brain dead donor (ND) hearts. Superior vena cava and tricuspid flow velocities were recorded as well as mitral and aortic flow velocities and left ventricular dimensions and wall thickness with a Hewlett–Packard Sonos 500/1000 ultrasound system. Simultaneous phonocardiogram and respiratory tracings were recorded. No significant differences in tricuspid or superior vena cava flow velocities were observed between the two groups (peak tricuspid flow at end expiratory apnoea, D 49 (9) cm/s *v* ND 53 (13) cm/s; tricuspid diastolic flow duration, D 178 (45) ms *v* 165 (38) ms; superior vena cava systolic flow velocity, D 26 (11) cm/s *v* 28 (9) cm/s; superior vena cava diastolic flow velocity, D 40 (7) cm/s *v* 43 (16) cm/s). In addition, superior vena cava flow velocity integrals and duration of superior vena cava systolic and diastolic flow were similar. This suggests that right sided filling as measured by Doppler flow is not altered by the use of right heart hypertrophied donor hearts when examined at long term follow up.

Heart rate and sudden death in cardiac transplant recipients

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There have been three late sudden deaths in the first 104 consecutive long term survivors ($\geq$three months) of orthotopic cardiac transplantation at this centre. Unexplained sinus tachycardia with a rate of $\geq$130 beats/minute had been observed in all three patients during routine follow up. We therefore retrospectively reviewed resting 12 lead electrocardiograms recorded at routine three monthly follow up and determined serial heart rates in all 104 survivors. Mean heart rates during 22 (13) months of follow up were 99·9 (16) beats/minute at three months; 100 (11·5) beats/minute at six and nine months; 101 (13) beats/minute at one year; 96·5 (11·6) beats/minute at two years; and 94·4 (10·5) beats/minute at three years. The mean heart rate during the follow up period was 104 (11) beats/minute. The mean heart rate was greater than the 95th centile (mean (2 SD)) in four patients, three of whom died suddenly. Postmortem examination in two of these three showed coronary artery disease. There were no other sudden deaths but four patients died of other causes. The heart rate was not related to either donor age or to rejection.

Thus, we have established a normal range for heart rate in the three years after cardiac transplantation and have shown that there is no significant change with time after transplantation. Three of the four patients with unexplained sinus tachycardia with a rate greater than the 95th centile died suddenly, compared with none of the 100 with heart rates within the usual range after transplantation. Unexplained sinus tachycardia may therefore be an adverse prognostic sign. The mechanism of such tachycardias is not known, although perhaps there is a relation with coronary artery disease.

Haemodynamic characteristics of patients assessed for single lung transplantation

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Single lung transplantation has been performed at this hospital since 1986. Twenty five patients with end stage respiratory disease (14 men, 11 women; mean age 46 years, range 20–58) have undergone preoperative assessment including measurement of right heart pressures, cardiac outputs, and pulmonary resistances. Right ventricular (RV) angiography was performed in 22 and coronary arteriography in 20. The aim of this retrospective study was to define the haemodynamic characteristics of such patients and to determine whether preoperative haemodynamic status predicted surgical outcome. Mean RV systolic pressure was 44 mm Hg and mean pulmonary artery pressure 30 mm Hg. Pulmonary hypertension was present in 24 patients (96%), being mild in 13 (54%), moderate in six (25%), and severe in five (21%). Mean pulmonary artery wedge pressure was 12 mm Hg. Mean cardiac index was 3·0 l/min/m^2, mean total pulmonary resistance 11·1 Units × m^2, and mean pulmonary arteriolar resistance 6·6 Units × m^2. Only six (27%) had normal RV function. Coronary disease was found in five patients (20%). The length of history and severity of hypoxia did not predict the degree of pulmonary hypertension. Eleven of these 25 patients received transplants (44%), with four dying in the first month. Survivors had more pulmonary hypertension (RV systolic pressure 53 *v* 41 mm Hg, mean pulmonary artery pressure 35 *v* 25 mm Hg, p = 0·024) but better cardiac indices (3·0 *v* 2·2 l/min/m^2) with lower total pulmonary resistance (12·5 *v* 15·3 Units × m^2) and pulmonary arteriolar resistance (8·3 *v* 8·9 Units × m^2). They tended to be older (49 *v* 45 years), and male patients did better in the early stages. The extent of RV dysfunction and coronary disease were similar in survivors and non-survivors. A further seven patients underwent transplantation without preoperative catheterisation.

These data define the population being assessed for single lung transplantation for end stage pulmonary disease. Pulmonary hypertension of variable severity is present in almost all and 73% have RV dysfunction. Transplantation is their only viable treatment option and the acute outcome seems to be better in those with lower pulmonary resistances despite the presence of more severe pulmonary hypertension.

Superior qualities of University of Wisconsin (UW) solution for ex vivo preservation of pig heart

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We evaluated UW solution by comparing it with St Thomas's solution (ST) in isolated pig hearts subjected to eight hours of ischaemia (n = 6 in each). The hearts were perfused ex vivo with autologous blood for control and post-preservation assessment. Morphological, metabolic, and functional evaluation was performed. Left and right function as assessed by slope values of systolic and diastolic pressure-volume relations of isovolumically contracting heart was better preserved by UW solution (% reduction: left ventricular systolic 52·4 (5·5) *v* 17·7 (6·7) (p < 0·001), left ventricular diastolic 125·6 (46·4) *v* 65·5 (31·4) (p < 0·05), right ventricular diastolic 112·3 (48·7) *v* 40·2 (31·3) (p < 0·02) after ST and UW preservation respectively). Post-ischaemic recovery of left ventricular dP/dt and MvO_2 were significantly improved after UW preservation (p < 0·001). Coronary vascular resistance was well maintained in the UW group as opposed to the significant increase in the ST group (p < 0·001). Preservation of myocardial ATP was improved and energy charge unchanged after eight hours of ischaemia and reperfusion in the UW hearts ($p < 0{\cdot}01$). Electron microscopic examination showed substantially better preservation of contractile apparatus after UW preservation.

These observations suggest that UW solution has the potential to improve the preservation of heart and possibly prolong the ischaemic period in clinical cardiac transplantation.

Haemoglobin-oxygen affinity in chronic heart failure

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In chronic left heart failure there is an impaired cardiac output response to exercise and increased arteriovenous oxygen extraction and infra red spectroscopic studies show profound oxygen desaturation within exercising muscle. The haemoglobin-oxygen dissociation curve is an important determinant of oxygen delivery to the tissues; there are adaptive changes in haemoglobin-oxygen dissociation in chronic hypoxic lung disease and at high altitudes due to changes in red cell 2,3-diphosphoglycerate content. Adaptive changes in haemoglobin-oxygen dissociation might be important in heart failure when blood flow to exercising muscle is limited. Blood samples were obtained from 15 patients with severe heart failure (New York Heart Association grades III–IV), normal resting blood gas concentrations, and lung function of ≥75% predicted values and from 10 age matched controls. All subjects underwent maximal treadmill exercise with respiratory gas analysis and pulse oximetry. Haemoglobin-oxygen dissociation curves were measured at standard pH 7·13 by tonometry, and each patient's curve was characterised by P_{50}, the partial pressure of oxygen at which the haemoglobin is 50% saturated with oxygen. Red cell 2,3-diphosphoglycerate content was measured by enzymatic assay. The haemoglobin-oxygen dissociation curve was shifted to the right in heart failure (P_{50} 34·1 (1·4) mm Hg *v* 30·6 (1·2) mm Hg in controls; $p < 0{\cdot}02$). As a result at a given Po_2 of 30 mm Hg, haemoglobin would release 60% rather than 50% of its oxygen. Red cell 2,3-diphosphoglycerate concentrations in heart failure were near the upper limit of normal but not statistically greater than in controls. P_{50} correlated weakly with exercise capacity as reflected by peak oxygen consumption $\dot{V}o_2$max ($R = -0{\cdot}37$, $p < 0{\cdot}05$) but not with the fall in oxygen saturation on exercise.

Thus in moderate to severe heart failure haemoglobin-oxygen dissociation shifts so as to favour oxygen unloading in the periphery. This may be partly due to a small increase in red cell 2,3-diphosphoglycerate as an adaptation to peripheral hypoxia.

Haemoglobin inhibits endothelium dependent relaxation in human coronary arteries in vivo

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The importance of endothelium derived relaxing factor (EDRF) in the control of coronary vasomotor tone has only recently been recognised. Endothelium dependent vascular relaxation and the release of EDRF in vitro is now well established. However, evidence to indicate its presence and importance in vivo is only circumstantial in human coronary arteries. We investigated the role of EDRF in the control of coronary vasomotor tone with the specific inhibitor free haemoglobin (Hb). We report the inhibition of acetylcholine induced coronary vasodilatation by free Hb in seven patients (six women and one man) with angiographically normal coronary arteries. After diagnostic cardiac catheterisation three minute coronary artery infusions were given as follows: acetylcholine 0·1 μM, acetylcholine 0·1 μM and Hb 1 μM, acetylcholine 0·1 μM and Hb 10 μM, and 1000 μg isosorbide dinitrate. These substances were infused into the left anterior descending coronary artery through a 2 French infusion catheter. Quantitative coronary angiography was performed after each infusion. Acetylcholine 0·1 μM increased left anterior descending coronary artery diameter from (mean (SEM) Student's test) 2·32 (0·12) to 2·78 (0·20) mm ($p < 0{\cdot}01$). Hb 1 μM and 10 μM reversed this effect to 2·11 (0·18) mm ($p < 0{\cdot}001$) and 2·29 (0·14) mm ($p < 0{\cdot}05$) respectively. Isosorbide dinitrate, an endothelium independent vasodilator, overcame the inhibitory effect of free Hb (1 μM and 10 μM) causing vasodilatation (3·04 (0·24) mm, $p < 0{\cdot}001$).

We conclude that Hb is an inhibitor of EDRF in vivo at concentrations that have been recorded in some pathological states. It may provide a useful tool for further investigation of EDRF in this and other vascular beds in humans.

Ventilatory abnormalities in chronic heart failure are improved by physical training

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In chronic heart failure (*a*) patients are commonly limited by leg fatigue and dyspnoea, (*b*) factors other than haemodynamic factors are important in determining the ventilatory abnormalities, and (*c*) there are widespread skeletal muscle changes. We hypothesised that patients with chronic heart failure were physically deconditioned, particularly in their legs, and that this placed significant limitations on their exercise capacity. We examined the effect of an exercise training programme on exercise capacity and on ventilatory performance in 22 patients aged 54–77 (mean 64 years) with chronic, stable (> three months) non-oedematous heart failure of ischaemic origin (13/9 in New York Heart Association class II/III). Mean frusemide dose was 81 mg, and nine patients were receiving angiotensin converting enzyme inhibitors. Lung function clinically and by chest *x* ray was normal. Initial tests excluded those with exercise induced arrhythmias and ischaemia and ensured reproducibility of baseline measurements. Patients were then entered in random order to a training or detraining first programme with crossover after eight weeks to the opposite arm. Training consisted of home based bicycle ergometry, 20 minutes/day for five days/week at 70–80% of their maximum heart rate. During detraining the bicycles were removed from patients' homes and they were asked to avoid exercise that induced fatigue or dyspnoea. At the end of each period they were assessed by an observer blinded to their training state. Assessment comprised upright bicycle exercise to exhaustion, with four minute 25 W stages, with gas analysis for minute ventilation (Vi), minute carbon dioxide production (Vco_2) and minute oxygen (Vo_2) consumption. Training increased exerise time from 14 to 16·4 minutes ($p < 0·02$) and peak Vo_2 from 14·1 to 15·4 ml/kg/minute ($p < 0·02$). Resting and matched submaximal workload minute ventilation decreased, though peak Vi was unchanged. Resting and submaximal oxygen consumption was unchanged. At most submaximal workloads carbon dioxide production decreased, though it increased at peak workload. The time taken to reach a respiratory quotient of 1 increased from 10·9 to 13·7 minutes. Respiratory pattern did not change, though there was a trend to larger tidal volumes and lower breathing rates. The slope of Vi plotted against the Vco_2 production decreased, and the ventilatory carbon dioxide equivalent (Vi/Vco_2 against workload, a measure of Vi normalised for carbon dioxide production and workload) started lower and reached a lower trough point later.

In chronic heart failure exercise training improves exercise capacity, lessens the hyperpnoea of exercise, and improves some markers of ventilatory efficiency.

Characterisation of blood flow through healthy and stenosed mitral valves by cine magnetic resonance velocity mapping

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Magnetic resonance imaging is not limited by acoustic windows and is capable of accurate blood flow velocity measurement, but it has not been previously used to assess valvar stenosis. We measured mitral blood flow with magnetic resonance (MR) phase shift velocity mapping in 10 healthy volunteers and in seven patients with mitral stenosis. Mitral flow direction was determined from a TE 14 ms FEER magnitude acquisition sensitive to signal loss from turbulence. Mitral flow velocity (TE 3·6 ms) was then acquired in two oblique planes, parallel and perpendicular to the axis of mitral flow. MR measurements were compared with those from Doppler echocardiography. Peak MR mitral flow velocity (mean (SD)) in early diastole was 68 (12) cm/s, and in atrial systole 39 (10) cm/s with a ratio of 1·9 (0·6). These agree with normal values obtained from Doppler echocardiography. In patients with mitral stenosis there was persistent flow throughout diastole, which was significantly higher than in normals. The average peak MR velocity measurement was 189 (47) cm/s compared with Doppler velocimetry 204 (56) cm/s. The values correlated well ($r = 0·91$).

Magnetic resonance velocity mapping is a new non-invasive method for measuring blood flow velocity through the mitral valve, characterising its pattern, and calculating pressure half time. This technique is complementary to other non-invasive investigations for assessing mitral valve disease and evaluating left ventricular diastolic function particularly when adequate Doppler measurements are difficult.

In vitro evaluation of commercially available intravascular ultrasound system: comparison of ultrasound and histological appearances

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The sensitivity and specificity of a currently available intravascular ultrasound (IVUS) system in identifying the presence and nature of intracoronary plaque was assessed in nine 2 cm sections of coronary artery and one section of aortocoronary bypass graft removed from cadavers. Perfusion fixation at arterial pressure maintained their morphology. Vessels were sutured to a supporting platform through which ran a Sonicath 4·8 French gauge 20 MHz ultrasound catheter connected to a Diasonics IVUS imaging system. A screw mechanism enabled the artery to be moved enabling imaging at predetermined sites. Indelible ink marked the orientation of the artery, which was then sectioned at the same level as the IVUS images. Sections were photographed with a scale and then prepared for histological examination. For the purposes of comparison each section was divided into four quadrants. Histology and IVUS findings were compared in 84 quadrants. Significant atheroma was present in 24 quadrants and IVUS successfully identified 12 of these. False positive diagnosis of atheroma was made in 12 quadrants, giving a sensitivity of 50% and a specificity of 81%. Apart from highly echogenic areas of calcification no conclusions about plaque structure and content could be drawn from the IVUS images. Lumen areas measured by IVUS were larger by a factor of 2·1 than those measured from the photographs. The photographic technique was compared with measurements from the histology specimens and there was close agreement between the techniques (difference $<20\%$, $r = 0·93$). The discrepancy between IVUS and optical techniques in lumen size and plaque detail may be due to poor resolution of the intima by IVUS as the system accurately measured the lumen area of similar sized plastic tubes. Useful plaque characterisation in small and medium sized coronary arteries is likely to require the use of higher ultrasound frequencies.

Detection of coronary disease by cross sectional echocardiography during dobutamine stress

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Forty nine patients undergoing cardiac catheterisation for suspected coronary disease (CAD) were studied while not taking antianginal treatment by cross sectional echocardiography during incremental dobutamine infusion (5, 10, 15, and 20 μg/kg/min, each dose for eight minutes). A 12 lead electrocardiogram (ECG) was taken each minute. Parasternal long and short axis and apical four and two chamber views were used. End points were a new wall motion abnormality (WMA), significant symptoms, ST depression or arrhythmia, target heart rate, or systolic blood pressure of 220 mm Hg. All had an exercise ECG on a different day. Coronary angiography showed CAD ($\geqslant 70\%$ stenosis) in 35. Fourteen patients had a WMA at baseline. No patient had distressing symptoms or important arrhythmia and none required intravenous β blocker. The peak rate-pressure product during dobutamine was 11 967 (3032), 15 851 (4348), 17 915 (3766), and

18 249 (3993) at 5, 10, 15, and 20 μg/kg/min respectively compared with 24 921 (6604) on exercise ($p < 0{\cdot}01$). Sensitivity and specificity of new WMAs for CAD was 63% (22/35) and 93% (13/14) respectively compared with 49% (17/35) and 71% (10/14) for dobutamine ECG and 74% (26/35) and 71% (10/14) for exercise ECG. Eleven of 14 patients with three vessel disease had a positive stress echocardiogram compared with 6/12 with single vessel disease; the lesion was correctly localised to left anterior descending or right coronary/circumflex territories in all six. Colour flow mapping (PRF 4 kHz, 2·5 MHz transducer) detected new transient mitral regurgitation in four patients, all with CAD; 18 had mild mitral regurgitation pre-test, making stress induced changes uninterpretable.

Dobutamine stress echocardiography is safe, well tolerated, and moderately sensitive particularly in severe CAD and can be used in those unable to exercise.

Relation between cyclic variation in echo amplitude and segmental shortening in normal and abnormal hearts

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To investigate the relation between cardiac cycle dependent variation in reflected myocardial ultrasonography and different manifestations of myocardial contraction, regional echo amplitude (EA) was evaluated from real time cross sectional echocardiographic images in 38 patients. The method used for acquiring echo amplitude images allowed the assignment of absolute values of echo amplitude by using the parietal pericardium as an in vivo standard for the setting of ultrasound gain. The 38 patients studied consisted of 19 normal controls, 11 patients with cardiomyopathy and impaired ventricular function, and eight patients with severe pulmonary hypertension and reversed septal motion. This enabled the influence of impaired left ventricular performance and abnormal wall motion on cyclic variation of echo amplitude to be assessed. An index of cyclic variation (CVI) was measured, which was defined as (end diastolic EA − end systolic EA)/end diastolic EA. This allowed the incorporation of background levels of EA into the measurement of cyclic variation. CVI was compared with left ventricular cavity dimension, fractional shortening, septal and posterior wall thickness, systolic wall thickening, patient's age, and heart rate. Stepwise regression analysis showed systolic wall thickening to be the most significant independent variable correlated with CVI for both septum and posterior wall ($r = 0{\cdot}68$, $p = 0{\cdot}0001$, septum; $r = 0{\cdot}69$, $p = 0{\cdot}0001$, posterior wall). The slopes and intercepts for both regression equations were similar, suggesting that the relation between CVI and systolic wall thickening was independent of position within the myocardial wall. Subgroup analysis showed normal controls, patients with cardiomyopathy, and patients with pulmonary hypertension to have similar slopes and intercepts for their individual regression equations, suggesting that this relation is independent of left ventricular performance and abnormal wall motion.

There therefore seems to be a quantitative relation between the extent of cyclic variation of EA and the degree of segmental myocardial shortening as measured by systolic wall thickening which is not significantly influenced by location within the myocardium, left ventricular performance, or wall motion.

Transoesophageal contrast echocardiography and colour flow mapping: methods of choice for detection of shunts at atrial level

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The detection of shunts at atrial level is important and a reliable means of diagnosis is required. Precordial contrast echocardiography is usually performed to detect such shunts. To investigate the advantages of transoesophageal echocardiographic techniques 167 consecutive patients were studied with both precordial and transoesophageal echocardiography, by using cross sectional imaging with contrast techniques (with and without a Valsalva manoeuvre) as well as colour flow mapping. A patent foramen ovale was diagnosed in 31 patients, an atrial septal defect in 11 (seven with bidirectional shunts), and a pulmonary arteriovenous fistula in three. All right to left shunts were detected with transoesophageal contrast echocardiography. With this as a gold standard, the sensitivity of combined precordial techniques was 37% and that of transoesophageal colour flow mapping 46%. All left to right shunts were detected by transoesophageal colour flow mapping. With this as a gold standard, the sensitivities of both precordial colour flow mapping and a transoesophageal negative right atrial contrast study were 27%.

We conclude that transoesophageal contrast echocardiography is the echocardiographic method of choice for the detection of a right to left shunt at atrial level that cannot be excluded by a negative precordial study or a negative transoesophageal colour flow map study. A left to right shunt at this level is best detected by transoesophageal colour flow mapping.

Significance of delayed recovery after digital exercise echocardiography

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The aim of the study was to assess the incidence and significance of persisting regional wall motion abnormalities (RWMA) after a symptom limited treadmill exercise test (modified Bruce) with digital exercise echocardiography (DEE). We studied 39 consecutive patients with known coronary artery disease, 14 with one vessel, 21 with two vessel, and four with three vessel disease. RWMA analysis was performed with an 11 segment protocol, and a total score was provided for a semiquantitative evaluation of wall motion (akinesis = 1, hypokinesis = 2, normokinesis = 3, dyskinesis = −1). Images were acquired and digitised on line before and immediately after exercise (< 1 minute) and at five and 10 minutes into the recovery period. DEE was considered to be positive when new or worsening RWMA were detected immediately after the exercise test. Sixteen (41%) patients had a positive DEE (5/14 with one vessel, 9/21 with two vessel, and 2/4 with three vessel disease). In 7/16 (43%) patients RWMA were still present at five minutes and in three out of 16 (19%) at 10 minutes into recovery. None of the patients with persistent RWMA at five and 10 minutes had single vessel disease, whereas three patients with two vessel and one with three vessel disease had early (< five minutes) normalisation. None of the 23 patients with negative DEE developed late RWMA. Patients with delayed RWMA recovery had similar exercise performance and wall motion score (27·5 (1·5) delayed *v* 27·4 (1·6) early) immediately after exercise to those of patients who had an early recovery.

In conclusion, persistent RWMA during recovery occurred in 43% of patients with positive DEE and were related to the presence of multivessel coronary artery disease.

Intravascular ultrasound evaluation of interventional procedures

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To evaluate the clinical use of intravascular ultrasound (IVUS) we studied six patients undergoing invasive cardiological procedures (three angioplasty, one atherectomy, one aortic valvoplasty, one coronary angiography). An 0·014 high torque floppy guide wire was positioned in the region of interest. A 20 MHz Meditech 4·8 French Sonicath was advanced over the guide wire and connected to a Diasonics intravascular ultrasound imaging system. The tip of the catheter must be filled with sterile water before use. All patients received 5000 units of heparin. Images were recorded on videotape and imaging was repeated after the interventional procedures. Satisfactory imaging was obtained in two patients in whom atheroma was visualised before and after angioplasty (one) and atherectomy (one). Failure to image was due to failure to cross a coronary stenosis (two), excessive movement of catheter (during valvoplasty), and failure of one imaging catheter due to incorrect filling of its tip. Several problems need to be addressed before the more widespread use of this technique can be advocated. The imaging plane of this catheter is 3·5 cm behind the tip because of the monorail design rendering imaging of distal vessels impossible, and fluid filling of the catheter tip is a delicate and time consuming operation. Although we were able to identify atheroma on the images, higher ultrasound frequencies will be needed to obtain useful information about intracoronary plaque composition.

IVUS allowed observation of the distribution and gross structure of plaques within the coronary arteries, although catheter movement prevented useful imaging of the aortic valve. In our experience the technique is safe and practical but further developments in catheter design are required before useful clinical data can be obtained on a regular basis.

Spontaneous variability of left ventricular function: assessment with a miniature nuclear probe (Cardioscint)

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Nuclear probes have been used for detecting rapid changes in left ventricular function, yet the normal, spontaneous variability in such measurements made at the bedside has yet to be clearly defined. Nine normal volunteers (eight men) of mean age 49 (SD 10) years underwent radionuclide ventriculography in the semisupine position. This was performed both with a γ camera and the Cardioscint, a non-imaging miniature nuclear probe, in randomised order. The camera recorded four consecutive images, each acquisition taking a mean of 7·3 minutes. The probe, with a 20 s gated acquisition time, recorded left ventricular function for about 35 minutes per patient. The mean ejection fraction of the group was 53% (7)% with the camera and 54% (5)% with the probe. When the variability in ejection fraction measured by the camera was compared with that measured by the probe averaged over corresponding time periods—that is, an average of 7·3 minutes—their mean coefficients of variation were similar (3·9% with the camera and 3·1% with the probe). Twenty second probe variability over the total acquisition time was also satisfactory with a coefficient of variation of 5·4%. In only two patients was this index of short term variability significantly greater than that of the camera despite the camera's longer acquisition time.

Thus the probe provides a stable recording of ejection fraction. These "normal" coefficients of variation may now provide a basis for the definition of pathological deviations.

Magnetic resonance assessment of aortic flow during dobutamine stress predicts extent of myocardial ischaemia

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In patients with coronary artery disease an abnormal response of global left ventricular function to stress is diagnostic and predicts prognosis. We examined the value of cine magnetic resonance (MR) velocity mapping during dobutamine stress in the assessment of parameters of aortic blood flow as indicators of ischaemia related ventricular dysfunction. We studied ascending aortic flow in five normal volunteers and 25 patients, 22 of whom had coronary artery disease. The extent of ischaemia was assessed by dobutamine/thallium myocardial perfusion tomography. MR imaging was performed at rest and during each of four stages of a dobutamine infusion from 5–20 μg/kg/minute. Stroke volume, cardiac output, peak flow, and peak flow acceleration were derived from the instantaneous flow measurements through the cardiac cycle. Between baseline and peak stress the change in peak flow acceleration was higher in controls than in patients with coronary artery disease (19·8 (3·5) *v* 10·8 (4·1), $p < 0·001$). The change in peak flow was also higher in controls (23·1 (3·4) *v* 16·3 (6·6), $p < 0·01$) but considerable overlap occurred between the two groups. Changes in stroke volume and cardiac output were not significantly different between the groups. There was an inverse linear relation between the increase in peak flow acceleration and the extent of myocardial ischaemia. A fall in peak flow acceleration during stress occurred only in patients with moderate or severe ischaemia ($p < 0·001$).

A failure to increase peak flow acceleration by 15 l/s^2 identified patients with coronary artery disease with 86% sensitivity and 86% specificity. The changes in peak flow acceleration predicted the extent of reversible ischaemia. A reduction in peak flow acceleration was indicative of moderate or severe myocardial ischaemia.

Isolation, culture, and characterisation of human cardiac microvascular endothelial cells

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Cardiac microvascular endothelium has been implicated in mediating myocardial hypoxic reperfusion injury. Endothelial cell heterogeneity may preclude the application of data from non-cardiac or animal endothelial cell in vitro studies to the situation in the human heart. We therefore performed the isolation, culture, and characterisation of human cardiac microvascular endothelial cells; this has not been previously described, perhaps partly because of the limited tissue availability and the fastidious nature of adult microvascular endothelial cells in culture. Fresh tissues were obtained from operative specimens (mitral valve papillary muscles, right atrial appendages (RAA), and whole cardiac explants). Endocardial and epicardial surfaces, fibrous tissue, and macroscopic blood vessels were excised. RAA endocardium was rendered non-viable by immersion in absolute alcohol followed by washing in Hank's balanced salt solution. Endothelial cells were isolated by mincing the tissue into 2 mm^3 pieces and incubating with a 0·5% crude collagenase solution containing 100 mM calcium chloride (to ensure non-viability of contaminating myocytes). Capillary segments were expressed from the digest with a flat spatula. Material was disaggregated and filtered through a 250 μm mesh to remove large tissue pieces. The filtrate was centrifuged and the pellet resuspended in culture medium and incubated at 37°C. After 24 hours the cells were washed and the medium replaced, thus removing debris and leaving the adherent endothelial cells. Confluent cultures were passaged every 10–14 days. The endothelial nature of the cultured cells was confirmed by electron microscopy, by characteristic granular staining for von Willebrand factor, and by staining with the endothelial cell specific monoclonal antibody QB–END/10. To ascertain the optimal site for endothelial cell extraction, source tissues were also immunostained with the above endothelial cell markers. Morphometric studies demonstrated that all tissues contained high endothelial cell densities. However, sections from the left ventricle were found to contain a significantly greater density of microvascular endothelial cells (mean 486 mm^2) than either RAA (mean 288 mm^2) or papillary muscle (mean 336 mm^2) ($p < 0{\cdot}05$ with a Student's *t* test). Thus when available left ventricular myocardium will be used to gain the maximum endothelial cell yield.

Ultrasonic tissue characterisation for detecting acute cardiac rejection in humans

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Myocardial echo amplitude was measured in 81 patients 12–2939 days (mean 473 (SD 575) days) after orthotopic cardiac transplantation. Patient age was 15–65 years (44·4 (12·3) years). A total of 105 echo amplitude studies were performed within 24 hours of right ventricular endomyocardial biopsy. Echo amplitude was determined by analysis of long axis parasternal cross sectional echocardiographic images acquired with a 3·5 MHz mechanical sector scanner. Each image was standardised by setting the master gain to display the posterior parietal pericardium at the highest level of echo amplitude and using linear depth compensation at 2 dB/cm. For analysis selected video frames were transferred from tape to a frame store and echo amplitude determined in areas of interest in the basal septum and left ventricular wall with the help of a computer. In 25 studies acute cardiac rejection was confirmed by histology. End diastolic myocardial echo amplitude was markedly and significantly increased in both the interventricular septum and posterior wall during acute rejection (septum, 9·7 (2·9) dB *v* 5·6 (2·0) dB; posterior wall, 10·0 (2·8) dB *v* 7·8 (2·2) dB; $p < 0{\cdot}001$). With a value of end diastolic echo amplitude in the septum of 6·9 dB as a marker of rejection, the sensitivity of this technique for detecting rejection was 94% and its specificity 79%. We suggest that this increase in myocardial echo amplitude is related to altered acoustic properties within the myocardium associated with the increased myocardial water content that occurs during acute cardiac rejection.

These data support the usefulness of myocardial echo amplitude as a non-invasive marker of cardiac rejection and show that it is possible to measure echo amplitude with modified commercially available echocardiographic equipment.

Magnetic resonance screening of cardiac transplant rejection by T2 parametric map of the left ventricle: correlations with endomyocardial biopsy

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This study evaluates the applicability of magnetic resonance imaging screening of cardiac transplant recipients as an alternative to serial right ventricular biopsy assessments of rejection. The myocardial pattern of T2 relaxation times was determined in eight patients who had received a cardiac transplant at least three months previously and in three control subjects. A 1·5 T system was used with aquisition in a parasaggital oblique section, yielding a short axis view of the ventricle midway between the apex and base. Each patient had undergone endomyocardial biopsy within five days of the magnetic resonance imaging (MRI) scan. The mean segmental T2 value in the control subjects was 37·2 (7·8) ms. Two patients had segmental T2 values in the normal range (< 52·8 ms) with no evidence of rejection on biopsy. Three patients had unequivocally raised T2 values (> 58 ms) in some segments of the left ventricle, with biopsy positive evidence of rejection. Two of these underwent repeat MRI after treatment of rejection, and the MRI maps returned to normal, as did the results on biopsy. Three patients had partial segmental T2 elevation with normal results on biopsy. These abnormal segments were distant from the biopsy sites and would be consistent with the patchy nature of the cardiac rejection process as observed in pathological studies.

We conclude that MRI may be a useful tool for the serial assessment of cardiac rejection, thereby reducing the rate and risks of invasive right ventricular biopsy. This method may also provide a more complete picture of the rejection process than has previously been possible.

Low phosphocreatine to ATP ratio detected in vivo in failing human hypertrophied myocardium by phosphorus-31 magnetic resonance spectroscopy

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Non-invasive detection of deterioration in cardiac metabolism would be valuable in deciding on the timing for surgery in patients with myocardial hypertrophy due to aortic valve disease. Phosphorus-31 magnetic resonance spectroscopy was therefore used to examine 17 patients, seven of whom complained of symptoms of heart failure due to either aortic stenosis (10) or aortic incompetence (seven). Spectra were collected by using a 1·9 Tesla 60 cm bore magnet and myocardial energy state was assessed from the ratio of the phosphocreatine (PCr) to ATP concentration. The left ventricular free wall thickness was similar in both groups (aortic stenosis, 1·6 (0·4) cm *v* aortic incompetence, 1·4 (0·4) cm; NS). Seven patients (ejection fraction 37·7% (17%)) were taking diuretics for symptoms of heart failure (New York Heart Association class I/II). The ratio of PCr to ATP in these patients (0·93 (0·16)) was lower than that in controls ($n = 13$, 1·5 (0·2); $p < 0{\cdot}001$) or in those who were not taking diuretics (1·52 (0·2); $p < 0{\cdot}001$). The ratio of phosphodiester to ATP (0·86 (0·2)) was not significantly different from that in controls (0·7 (0·16)).

These findings indicate that the ratio of PCr to ATP is a sensitive marker of impairment in cardiac metabolism in patients with myocardial hypertrophy who require treatment for fluid retention. The role of this index in determining the optimum time for aortic valve replacement is being examined.

Long term prognostic significance of total ischaemic burden and silent ischaemia in patients with unstable angina stabilised with medical treatment

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The aim of this study was to assess the long term prognostic significance of total ischaemic burden and silent ischaemia in 76 patients with unstable angina stabilised with medical treatment. All patients underwent Holter monitoring for at least 48 hours, beginning during the first 12 hours after hospitalisation. Total ischaemic burden $\geqslant 60$ minutes was present in 43 patients (group A) while 33 patients (group B) had a total ischaemic burden $\leqslant 60$ minutes. Over 78% of the ischaemic episodes of patients in group A and 62% of those of patients in group B were silent ($p < 0{\cdot}05$); nine patients in group A and six in group B had only silent episodes. Patients in group A frequently showed three vessel disease (65% *v* 18%, $p < 0{\cdot}01$), angiographical findings of subocclusion of the coronary arteries (grade TIMI I) (76·7% *v* 42·4%, $p < 0{\cdot}01$), and ischaemic alterations in a resting electrocardiogram (51·2% *v* 30·3%, $p < 0{\cdot}05$). During six years of follow up 15 patients in group A and eight patients in group B experienced myocardial infarction ($p < 0{\cdot}01$); nine patients in group A and four in group B required coronary artery surgery ($p < 0{\cdot}05$) and 10 patients in group A and four in group B died from cardiac causes ($p < 0{\cdot}001$). The Cox's proportional function analysis showed three vessel disease to be the most important predictor of cardiac mortality and morbidity ($p = 0{\cdot}025$), followed in predictive power by a total ischaemic burden $\geqslant 60$ minutes. The presence of silent ischaemia was not an independent predictor of long term morbidity and mortality.

In conclusion, patients with unstable angina and total ischaemic burden $\geqslant 60$ minutes have frequently silent ischaemic episodes on Holter monitoring, a greater extent of coronary atherosclerosis, and ischaemic alterations in the resting electrocardiogram. The long term prognosis of patients with unstable angina stabilised with medical treatment depends on the extent of coronary atherosclerosis and total ischaemic burden but not on the presence of silent ischaemia.

Adjuvant xamoterol or metoprolol for control of amiodarone resistant ventricular tachycardia in patients with impaired left ventricular function

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β Blockers may be effective in combination with amiodarone in controlling ventricular tachycardia (VT) but are often limited by their negative chronotropic and inotropic effects, particularly in patients with left ventricular (LV) dysfunction. Use of xamoterol, a partial β agonist, may avoid some of these drawbacks. The antiarrhythmic efficacy of xamoterol and metoprolol as adjuvant treatment to amiodarone was assessed by a randomised crossover study in 19 patients with LV dysfunction (ejection fraction <30%) and recurrent sustained VT (incessant in four cases) despite treatment with amiodarone for >2 weeks and other drugs (2–7, median four failures). The three regimens (amiodarone, xamoterol and amiodarone, and metoprolol and amiodarone) were compared by programmed electrical stimulation and exercise testing. Five patients were unable to tolerate metoprolol and one was unable to tolerate xamoterol because of haemodynamic deterioration. The combination of xamoterol and amiodarone was more effective than amiodarone alone or metoprolol and amiodarone in controlling VT induced at programmed electrical stimulation ($p < 0{\cdot}02$). Overall, xamoterol and amiodarone produced complete or partial suppression in 13 out of 19 patients with inducible VT with amiodarone alone, although there was no significant change in ventricular effective refractory period or tachycardia cycle length. Both combinations of xamoterol with amiodarone and metoprolol with amiodarone reduced peak heart rate on exercise compared with amiodarone (108 (15) and 98 (16) *v* 128 (19) beats/minute; $p < 0{\cdot}01$) and suppressed exercise induced VT in three out of four cases. Eleven patients were discharged taking xamoterol and amiodarone and one taking metoprolol and amiodarone. During follow up (1–24 months) recurrent VT developed in two patients within six weeks and in one patient at 11 months. The remainder were free of tachycardia.

We conclude that xamoterol is more effective and better tolerated than metoprolol as adjuvant treatment for controlling amiodarone resistant VT in patients with poor LV function. Even in patients with antitachycardia devices xamoterol and amiodarone may be of value in reducing the frequency of attacks and facilitating tachycardia recognition by rate criteria.

Predictors of induced arrhythmia suppression and long term efficacy of oral sotalol in patients with drug refractory ventricular arrhythmias

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Predictors of efficacy of sotalol, a β adrenergic receptor blocking agent with class III antiarrhythmic action, were evaluated in 161 patients with drug refractory ventricular arrhythmias. There were 138 men and 23 women aged 20–88 (mean 61) years. The majority (89%) had coronary artery disease and the mean left ventricular ejection fraction was 41% (SD13%). Their presenting clinical arrhythmia was ventricular tachycardia (VT) in 115, ventricular fibrillation (VF) in 28, and symptomatic non-sustained VT (NSVT) in 18. Sotalol was not used in patients with uncompensated heart failure, a left ventricular ejection fraction of less than 20%, or severe bronchospasm. In 39 out of 131 patients with sustained ventricular arrhythmia induced by programmed stimulation sotalol suppressed the arrhythmia. Multiple regression analysis of clinical variables identified four factors associated with suppression of induced arrhythmia by sotalol: (*a*) the clinical arrhythmia ($p < 0{\cdot}0005$), (*b*) the absence of coronary artery disease ($p < 0{\cdot}05$), (*c*) a higher left ventricular ejection fraction ($p < 0{\cdot}05$), and (*d*) a shorter cycle length of the induced arrhythmia before drug treatment ($p < 0{\cdot}05$). The best multivariable model used only the arrhythmia and coronary artery disease as independent predictors of arrhythmia suppression, with a predictive accuracy of 74%. For example, the probability of arrhythmia suppression by sotalol for patients presenting with VT, VF, and NSVT was 21%, 59%, and 73% for patients with coronary artery disease and 52%, 92%, and 96% for those without. Seventy seven patients were discharged taking long term oral sotalol. Patients were followed up for a maximum of five years (mean 18·3 (SD 15·6) months). There were five sudden deaths and 10 recurrences of non-fatal sustained arrhythmia and four patients had symptomatic NSVT. Actuarial life table analysis showed that arrhythmia free survival was 88% at six months, 78% at one year, and 65% at two years. Multivariable analysis identified persisting inducibility, clinical arrhythmia, and age as predictors of recurrence. Event free survival at two years for patients with no inducible VT or VF with sotalol treatment was 85% and for those still inducible it was 49% ($p < 0{\cdot}05$). Seventeen out of 28 (61%) patients with VF at presentation were treated with long term sotalol with no recurrence of arrhythmia during a mean follow up of 22 months.

In conclusion, clinical VT and coronary artery disease are predictors of persisting arrhythmia inducibility with sotalol treatment, which in turn is a predictor of arrhythmia recurrence. When inducible VT or VF is suppressed sotalol provides effective long term treatment, especially for patients presenting with VF.

Surgical management of arrhythmogenic right ventricular dysplasia

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Arrhythmogenic right ventricular dysplasia (ARVD) is a rare but important cause of ventricular tachycardia (VT), particularly in young males. Ten patients (nine men, mean age 39 years) with ARVD underwent surgery for arrhythmia control. All were refractory to medical treatment and treatment with a minimum of three drugs (mean five), including amiodarone, had failed. All had a history of syncope and six had a history of cardiac arrest; three had a family history compatible with ARVD. At operation the right ventricle (RV) was grossly diseased. Sustained monomorphic or multimorphic VT was induced and mapped intraoperatively in all patients. One patient underwent cryoablation of an arrhythmogenic focus in the upper part of the RV septum. A disarticulation procedure was performed in the remaining nine and was partial (approximately 40% of the RV free wall) in four and total (complete electrical isolation of RV from LV) in five. During mean follow up of 21 months three patients had recurrences of VT of new configuration. All were well tolerated and easily controlled by drug treatment. Four of the nine patients who underwent RV disarticulation experienced postoperative heart failure but all improved progressively with the development of paradoxical septal motion. All 10 patients were arrhythmia free and their condition was New York Heart Association functional class I/II at last review.

Surgery effectively controls VT related to ARVD. It should be recommended to patients with ARVD whose arrhythmias are posing a threat to life or are frequent despite drug treatment.

Management of refractory ventricular arrhythmias: endocardial resection or implantable defibrillator?

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During an 18 month period 20 consecutive patients, all men (mean age 62 (15) years, range 55–70) were treated with antiarrhythmic surgery or an implantable cardioverter defibrillator (ICD) for malignant ventricular arrhythmias. Nineteen patients underwent myocardial revascularisation (CAVBG or LIMA (n = 2)). In addition, eight patients had map guided endocardial resection (MGER), in two of whom cryoablation was also performed. Two patients had left ventricular aneurysmectomy. Three patients died (38%) postoperatively of pump failure. Epicardial patches were inserted in three of the five survivors, all of whom were non-inducible 10 days after operation, and there have been no recurrent arrhythmias at a mean follow up of 13 months (range 5–20). Twelve patients were selected for ICD. Two patients died postoperatively of pump failure and one patient was non-inducible after CAVBG alone. Nine patients received an ICD. All patients were alive at a mean follow up of 11 months (3–17). One patient developed atrial flutter 12 months after implantation causing inappropriate defibrillation.

Although the study group is small, the results suggest that in addition to myocardial revascularisation, MGER is indicated in monomorphic VT. ICD should be reserved for cases with poor left ventricular function, infrequent arrhythmias, and inferior scars where endocardial resection is technically difficult.

Antitachycardia pacemaker/automatic implantable cardioverter defibrillator in patients with frequently recurring ventricular tachycardia

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Ventricular tachycardia which recurs frequently is a relative contraindication to implantation of an automatic implantable cardioverter defibrillator (AICD) because of multiple shocks and battery depletion. Antitachycardia pacing is an alternative treatment, but pacing may acclerate arrhythmias. An automatic implantable programmable device (Ventritex V-100) which delivered tiered therapy (antitachycardia pacing, low energy or high energy shocks) in response to detected arrhythmias was studied in 22 patients with drug refractory recurrent ventricular tachycardia. There were 20 males and two females, aged 14 to 78 (mean 61) years. Twenty had coronary artery disease. Mean left ventricular ejection fraction was 32%. Non-invasive programmed stimulation after device implantation confirmed successful termination of induced ventricular tachycardia by antitachycardia pacing in 19 patients, failure of antitachycardia pacing in two, and induction of rapid ventricular tachycardia terminated by cardioversion in one. Acceleration of induced ventricular tachycardia by antitachycardia pacing was observed in four patients. During follow up of 1–13 months (mean 5·8 months) there were no deaths. Spontaneous ventricular fibrillation and ventricular tachycardia recurred in one and 16 patients, respectively. The time interval to recurrence of ventricular tachycardia ranged from three days to four months (mean 4·6 weeks) and was less than one month in 11 patients. Assessment of arrhythmias and therapy delivered was obtained by interrogation of the device and retrieval of stored intracardiac electrograms. The number of episodes of ventricular tachycardia per patient ranged from one to 150. Six patients had more than 50 episodes within five months. Rates of spontaneous tachycardia ranged from 130 to 210 beats/minute (mean 157 beats/minute). Spontaneous ventricular tachycardia was terminated by antitachycardia pacing in 15 out of 16 patients, in 87% of episodes. Acceleration of ventricular tachycardia by antitachycardia pacing was documented in eight patients, with ventricular fibrillation in 13 episodes. In only two of these eight patients had acceleration of patients had acceleration of ventricular tachycardia by antitachycardia pacing been demonstrated at previous non-invasive programmed stimulation. Failure of antitachycardia pacing was observed in five patients, but in only one was it never successful. Eight patients received shocks for ventricular arrhythmias. Inappropriate therapy was delivered in eight patients (during sinus tachycardia in two and atrial fibrillation in five and because of sensing lead fracture in one), with five of the eight receiving inappropriate shocks. Failure to detect ventricular tachycardia occurred in two patients because the tachycardia rate was below the detection rate.

In conclusion, antitachycardia pacing is effective in terminating ventricular tachycardia in patients with frequently recurring arrhythmia. Acceleration to life threatening arrhythmias, which require high energy shocks, may not be predicted by responses to induced arrhythmia.

Recognition of ventricular tachycardia by intracardiac electrogram cross phase spectra

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A mathematical theory of ventricular tachycardia (VT) recognition for use in implantable devices has been developed that separates electrograms into components determined by the activation sequence and components due to action potential (AP) shape which may be discarded. The delays in depolarisation of individual myocytes result in a linear phase shift with frequency in the Fourier series (FS) of their APs. The FS of the recorded electrogram can be calculated by summation of the FS of all the APs in the electrode receptive field after weighting their amplitudes to account for their distances from the electrode and intervening tissue resistances and geometry. The difference in the phase of the FS of electrograms at two sites in the ventricle, the cross phase spectrum, depends on the relative delays in activation of myocytes in the two receptive fields and is independent of the AP morphology, provided that its dispersion within the electrode receptive field is small. This gives a theoretical basis for using the cross phase spectrum to detect the changes in activation between sinus rhythm and VT. Right ventricular bipolar electrograms were obtained in 24 episodes of VT in 21 patients with ischaemic heart disease and cardiomyopathy (three spontaneous, eight exercise induced, and 13 programmed stimulation), during exercise in 12 patients and over 24 hours in nine. The cross phase spectrum in sinus rhythm and during VT fell into separable distributions in 22 episodes. Studies of exercise induced and long term variability of the cross phase spectrum show that an adaptive template is required as the use of a static sinus rhythm template to detect VT would result in more than 50% non-specificity.

The cross phase spectrum is a highly sensitive method of detecting activation sequence changes during VT, but the physiological variability of intracardiac electrograms requires that adaptive methods of detecting abrupt changes in the cross phase spectrum are implemented to avoid false positive detection of VT.

Heterotopic heart transplantation in ischaemic heart disease: role of adjunctive surgery to recipient heart

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The role of heterotopic cardiac transplantation in coronary heart disease has not been defined. Between 1983 and 1988 a group of 28 patients with end stage ischaemic heart disease was managed by heterotopic heart transplantation and adjunctive surgery to the recipient heart (coronary artery bypass grafts and aneurysmectomy 20, coronary artery bypass grafts five, and aneurysmectomy three). Indications were feasibility of operative procedures to the recipient heart and small donor size (54% of the donors < 15 years). There were six deaths. The one year and five year actuarial survival was 79% and 63%. Of the 22 patients who survived to two years of follow up, all of whom were severely limited (New York Heart Association grade III/IV) preoperatively, 20 were in categories I or II at two year follow up ($p < 0\cdot0001$). Only one experienced angina at two years compared with 15 preoperatively ($p < 0\cdot001$). In 14 out of

22 (64%) patients the recipient heart augmented the donor cardiac output significantly, and in four the recipient heart supported the patient when the donor heart failed to eject. The coronary artery bypass graft patency was 79% (23/29) at two years and 50% (8/16) at five years. Thromboembolic complications were rare (transient ischaemic attacks in two patients). The incidence of accelerated coronary artery disease in donor hearts was 9% (2/22) at two years and 36% (4/11) at five years.

In conclusion, this series shows the efficacy of heterotopic transplantation combined with surgery to the recipient heart in managing patients with end stage ischaemic heart disease.

β Adrenoceptor density in donor heart: a guide to prognosis?

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Early intractable cardiac failure unrelated to rejection is a recognised complication of orthotopic cardiac transplantation. Donor hearts are usually obtained from brain dead subjects dying in situations in which myocardial damage is known to occur via excess activation of the sympathetic adrenergic pathway. β Adrenoceptor density down regulation is related to excess catecholamine exposure and a reduction in the density seems to contribute to the reduced physiological responsiveness of the failing heart. To test whether there is a relation between β adrenoceptor density in the donor heart and the outcome for the recipient we retrospectively examined 31 donors not requiring inotropic support in whom right ventricular endomyocardial biopsy specimens had been obtained immediately before implantation. Radioligand binding saturation isotherms with 125-iodopindolol were performed on homogenate preparations and receptor density was determined with a non-linear regression curve fitting programme. Total β adrenoceptor density in the donor heart biopsy specimens where the recipient developed cardiac failure immediately after transplantation and died in the perioperative month was significantly lower than that in the successful donors where the recipient survived for at least six months (14 (2) fmol/mg protein (n = 8) *v* 22 (1·5) fmol/mg protein (n = 23), $p < 0·05$ Mann–Whitney–Wilcoxon).

This study suggests that evaluation of β adrenoceptor density in the donor myocardium may help to identify hearts associated with a poor surgical outlook.

Hypomagnesaemia and myocardial magnesium depletion after cardiac transplantation

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Hypomagnesaemia is associated with cyclosporin used after organ transplantation. There are no data pertaining to the magnesium (Mg) state of cardiac transplant recipients. Prospectively we studied 12 consecutive patients who underwent cardiac transplantation between January and June 1990. Serum and myocardial Mg content were measured at the time of endomyocardial biopsy at two weeks and three months after transplantation. In the six patients who received transplants earlier in the year measurements were repeated at six months. Myocardial Mg was measured in a single myocardial biopsy specimen by atomic absorption spectrometry and expressed as µmol Mg per gram dry weight myocardium. Serum Mg fell significantly from a mean (SD) of 0·74 (0·12) at two weeks after transplantation to 0·61 (0·08) mmol/l at three months ($p < 0·002$; paired *t* test). At three months 50% of patients were significantly hypomagnesaemic (serum Mg < 0·60). One patient developed disabling neurological signs of Mg deficiency (blood cyclosporin was within the therapeutic range), which responded dramatically to treatment with intravenous Mg sulphate. Myocardial Mg concentrations were similarly affected, with a mean myocardial Mg of 32·2 (4 7) µmol/g at two weeks falling to 29·4 (3·9) at three months ($p < 0·04$). In two patients myocardial Mg concentrations were severely depressed at two weeks (<25 µmol/g), remaining substantially unchanged over subsequent weeks. In the patients followed up for six months mean serum Mg concentration had risen slightly but was still depressed at 0·65 (0·09) mmol/l (two weeks *v* six months; NS), with four out of six patients remaining hypomagnesaemic. There was a suggestion of further myocardial Mg depletion (27 4 (5·2) µmol/g; $p < 0·06$), and in only one patient was the rise in serum magnesium concentration over the three to six month period paralled by an increase in myocardial Mg content.

We have shown that hypomagnesaemia and myocardial Mg depletion occur commonly in the post-transplant period. Serum Mg concentration tends to normalise six months after transplantation, but this is not accompanied by myocardial Mg repletion in most cases. Further studies are needed to investigate the clinical consequences of this observation and to establish the mechanism of Mg loss.

Functional assessment of left ventricular performance in transplanted human hearts

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Denervation of the heart in animals alters myocardial substrate handling and may influence myocardial mechanical efficiency. To investigate mechanical performance in the denervated human heart, left ventricular (LV) mechanical efficiency was calculated from LV heat production and LV energy supply (oxygen utilisation) in five patients who had undergone orthotopic cardiac transplantation. This was compared with LV mechanical efficiency in a control group of eight patients with non-cardiac chest pain. The transplant recipients were male, aged 39–53 (mean 44 5) years and had undergone transplantation 1–3 (median 2) years earlier. None had clinical or histological evidence of rejection and none was taking cardioactive drugs. The control group (four men, four women) were aged 37–71 (mean 53·5) years. All patients had normal LV function (ejection fraction 0·63 (0·06) in the controls and 0·67 (0·03) in the transplant recipients, NS) and normal epicardial coronary arteries. Energy supply to the myocardium in each group was similar (4·4 (1 7) *v* 4·7 (0·4) W, NS), but more energy was wasted as heat in the transplant recipients (2·4 (1 0) *v* 3 6 (0·4) W, p = 0·02). LV mechanical efficiency was reduced in the transplant group to 24·6% (3·8%) compared with 44·2% (9·6%) in the controls (p = 0·001).

Despite the normal clinical and angiographic findings, there is evidence that LV energetics are abnormal in transplanted human hearts. Whether the mechanism is due to denervation is unclear, but the reduced mechanical efficiency of the left ventricle in transplanted human hearts may have important long term clinical implications.

Doppler echocardiographic studies of flow in the superior vena cava: a sensitive and specific marker of acute cardiac rejection

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Doppler echocardiographic studies of superior vena cava (SVC) and pulmonary vein flow have shown a significant increase in the ratio of diastolic to systolic flow in patients with myocardial restriction. As changes resembling those seen in myocardial restriction have been observed during acute cardiac rejection, SVC Doppler flow was evaluated as a marker of acute rejection after orthotopic cardiac transplantation. Eighteen patients were studied, of whom six (heart rate 104 (SD 16) beats/minute; age 54 (5) years; time since transplantation 6·3 (11·7) months; ischaemic time 167 (60) minutes; donor age 31 (10) years) had histological criteria of rejection on endomyocardial biopsy performed within 24 hours. The remaining 12 patients (two women, heart rate 91 (15) beats/minute; age 51 (9) years; time since transplantation 15 (13) months; ischaemic time 122 (47) minutes; donor age 30 (8) years) were free from rejection. Pulsed wave Doppler studies of SVC flow were recorded in the supine position with a 5 MHz transducer and a Hewlett–Packard Sonos 500/1000 ultrasound system. Simultaneous phonocardiogram and respiratory tracings were recorded. Peak flow velocities (PFV) and flow velocity integrals (FVI) of SVC systolic and diastolic forward flow were measured. In the rejection group a marked and significant fall in systolic PFV compared with that in the non-rejection group was observed during all phases of respiration (6·8 (7·7) cm/s *v* 26·8 (9·8) cm/s ($p \leqslant 0{\cdot}001$) at end expiratory apnoea; 14·1 (21·1) cm/s *v* 33·4 (17·2) cm/s ($p \leqslant 0{\cdot}05$) at end inspiration; 9·4 (7·6) cm/s *v* 22·1 (9·0) cm/s ($p \leqslant 0{\cdot}02$) at end expiration). Importantly, the pattern of SVC flow did not seem to be affected by the timing of recipient atrial activity. If a value for SVC systolic flow velocity of $\leqslant$17 cm/s at end expiratory apnoea is chosen as indicating rejection then sensivity was 100%, specificity 75%, and predictive accuracy 83%.

These changes in SVC flow probably reflect restricted right ventricular filling due to myocardial oedema associated with acute rejection. Thus the examination of SVC flow provides a sensitive and specific marker of acute cardiac rejection.

Demonstration of proliferating cell nuclear antigen in myocardial biopsy specimens after cardiac transplantation

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Proliferating cell nuclear antigen (PCNA) is the polymerase δ accessory protein required for nuclear DNA synthesis. Specific monoclonal antibodies to PCNA can be used on histological sections to identify cells that are about to proliferate. PCNA containing cells were counted in the myocardial biopsy specimens taken in the management of cardiac transplantation. Positive marking was observed in up to 5% of myocyte nuclei, beginning with the first biopsy specimen taken at two weeks and continuing until a steady clinical state was reached. Positive nuclear marking was also seen in the interstitial connective tissue cells and in lymphoreticular cells during episodes of rejection. The number of positive cells correlates with the degree of rejection by conventional histological criteria. Severe rejection with myocytolysis was associated with positive counts of over 200 nuclei per mm^2 of tissue. Initiation of treatment caused a very rapid decline in the number of positive cells and occurred before the interstitial cellularity declined. Analysis of biopsy specimens preceding an episode of rejection did not show an increase of positive cells.

The presence of PCNA positive cells is thus not a sensitive means of predicting subsequent rejection but can confirm that rejection has been controlled.

Fibrinolytic treatment for unstable angina: double blind placebo controlled trial with alteplase

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In patients with acute unstable angina subtotal thrombotic coronary occlusion has been described. We studied 80 consecutive patients (56 male, mean age 61 years) with acute angina at rest ($\geqslant$15 minutes) and ST segment depression of $\geqslant$1 mm in any electrocardiogram lead. Twenty nine patients had had a previous myocardial infarction. All patients received oral aspirin and intravenous heparin and were randomised to group A (alteplase 100 mg) and group B (placebo) given over three hours. Within three days of admission coronary arteriography in 37 out of 40 patients from each group showed similar significant coronary lesions ($\geqslant$50% luminal stenosis)—eight patients with single vessel, 14 with double vessel, and 14 with triple vessel disease in group A compared with seven patients with single vessel, 13 with double vessel, and 13 with triple vessel disease in group B. Five patients had no coronary stenoses (one in group A, four in group B) and there were four left main stem stenoses (one in group A, three in group B). The ischaemia related vessel was patent (TIMI 2 or 3) in 31 out of 37 (84%) patients in group A and 29 out of 37 (78%) in group B. Myocardial infarction occurred in 26 patients in group A (13 non-Q wave, 13 Q wave) and in 24 patients in group B (19 non-Q wave, five Q wave). Thirty patients did not develop myocardial infarction. The left ventricular ejection fraction was 48% (range 17–69%) in group A and 56% (range 31–81%) in group B. Eight patients in each group required percutaneous transluminal coronary angioplasty and four patients in group A and five in group B required coronary artery bypass grafting during their stay in hospital. There were seven deaths (four in group A and three in group B).

Thus in patients with unstable angina (rest pain) receiving aspirin and heparin alteplase did not significantly improve patency in the ischaemia related vessel. The requirement for percutaneous transluminal coronary angioplasty and coronary artery bypass grafting was similar in both groups.

Streptokinase resistance titre and antistreptokinase IgG do not influence fibrinolytic efficacy of streptokinase containing thrombolytic agents

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Previous streptococcal infections and treatment with streptokinase containing agents induce an antibody response that may increase resistance to future treatment with these agents. This study examines the influence of baseline antistreptokinase IgG concentrations and streptokinase resistance titres on parameters of fibrinolysis and thrombin activity. Eighty two patients (40–74 years) presenting within six hours of onset of acute myocardial infarction were treated with either 1·5 MIU streptokinase as a 60 minute continuous intravenous infusion (n = 41) or 30 units of anistreplase (n = 41) as a five minute intravenous injection. Pretreatment streptokinase resistance titres (n = 54) and specific antistreptokinase IgG concentrations (n = 82) were measured. The distributions of both parameters were skewed toward low values (streptokinase resistance titre: median 50, interquartile range 20–100 IU streptokinase m^{-1}; antistreptokinase IgG: median 0·965, 0·472 – 1·903 μg streptokinase binding ml^{-1}). Venous blood was collected at frequent intervals from predosing to five days, immediately separated, and frozen for subsequent analysis for D-dimer and BB 15–42 fragment as indices of fibrinolysis. BB 15–42 and D-dimer release was calculated by measuring the area under the time activity curves. No significant relation between the measured area under the curve and pretreatment streptokinase resistance titre or antistreptokinase IgG was observed. In the range observed these indices of previous exposure to streptococcal protein do not inhibit the in vivo fibrinolytic action of streptokinase containing thrombolytic agents, suggesting that redosing with these agents may be possible earlier than has been recently suggested.

High concentrations of apolipoprotein (a) impair thrombolysis with alteplase in acute myocardial infarction

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Apolipoprotein (a) (Apo(a)) has marked structural similarity to plasminogen and has been shown to interfere with clot lysis in vitro. We have therefore assessed the relation between Apo(a) concentrations and coronary artery patency after thrombolytic treatment for acute myocardial infarction. Forty four subjects were seen within six hours of an acute myocardial infarction and were given two bolus injections of human recombinant tissue-type plasminogen activator (rt-PA, alteplase) separated by 30 minutes (total dose 70 or 100 mg). Coronary patency was assessed at 90 minutes by angiography and did not differ significantly between dosage regimens. Apo(a) concentrations were measured at 0, six hours, and 24 hours with a double monoclonal antibody immunoradiometric assay. Groups were compared with the Mann–Whitney U test. Subjects with patent coronary arteries (n = 35) had significantly lower Apo(a) concentrations than those with occluded coronary arteries (n = 9) (at 0 hours 270 u/l median range (15–1375) *v* 504 (65–1625), p = 0·028; at six hours 236·5 (15–1420) *v* 598·5 (72–1400), p = 0·044; at 24 hours 251·5 (12–1220) *v* 539 (63–1460), p = 0·041). Apo(a) did not change significantly in either group over the 24 hour period.

These results indicate that Apo(a) may significantly impair the thrombolytic action of rt-PA at physiological concentrations in vivo.

Increased exercise capacity after nebulised diamorphine in chronic heart failure

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To investigate whether nebulised opiate, through a peripheral action on pulmonary afferent C fibres, may modify the sensation of dyspnoea and improve exercise capacity in chronic left ventricular failure, eight male patients (mean age 60 years, range 52–74) in New York Heart Association class II underwent maximal treadmill exercise testing with respiratory gas analysis. After baseline exercise testing nebulised inhalations of placebo or 5 mg diamorphine were given over 15 minutes in a randomised, double blind manner. These were delivered via a modified Acorn system nebuliser to ensure small droplet size (1 μm) and peripheral airway deposition. Patients exercised immediately after nebulisation, and dyspnoea was assessed with a 100 mm visual analogue score. There was a significant increase in maximal oxygen consumption (Vo_2max) in ml/min/kg from 16·7 (3·3) at baseline to 17·7 (3·6) with diamorphine (p < 0·05). There was a significant increase in exercise duration from 641 (191) s at baseline to 734 (175) s with diamorphine (p < 0·05). There was no difference in ventilatory equivalent for carbon dioxide production slope (VE/Vco_2) or in the visual analogue score at a Vo_2 of 10 ml/min/kg or at maximal exercise with diamorphine compared with baseline.

Thus, finely nebulised diamorphine increases maximal exercise capacity and exercise duration in chronic left ventricular heart failure but with no reduction in the sensation of dyspnoea.

Chronic angiotensin converting enzyme inhibition does not improve aerobic exercise capacity after myocardial infarction

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In a double blind study 99 patients were randomised to receive placebo or captopril within 24 hours of acute myocardial infarction. Treatment was continued for one year, during which serial exercise tests were performed. The groups were well matched at baseline. At 12 months 35 patients taking captopril and 32 placebo completed symptom limited maximal cardiopulmonary treadmill exercise tests. Although the patients taking captopril had a significantly higher resting left ventricular ejection fraction, there was no difference between the groups in any of the following exercise parameters: peak heart rate (139 (SD 23) *v* 135 (24) beats/minute, $p = 0{\cdot}57$), peak systolic blood pressure (163 (25) *v* 167 (26) mm Hg, $p = 0{\cdot}61$), exercise time (448 (209) *v* 435 (176) s, $p = 0{\cdot}78$), peak oxygen consumption (23·1 (6·1) *v* 22·2 (5·5) ml/min/kg, $p = 0{\cdot}56$), peak carbon dioxide production (22·4 (7·1) *v* 22·7 (7·3) ml/min/kg, $p = 0{\cdot}87$), and peak ventilation (59·1 (20·2) *v* 62·6 (19·3) l/min). Exercise provoked ST segment depression of at least 1 mm in 11 patients taking captopril and nine taking placebo. There was no difference in the time to 1 mm ST segment depression between the groups. Captopril was withdrawn and the patients re-exercised one month later with similar results.

We conclude that in this group of patients after infarction one year's treatment with captopril had no effect on aerobic exercise capacity.

Randomised double blind placebo controlled trial of nimodipine in 1215 patients with acute stroke

J J Murphy for TRUST Study Group
Department of Medicine, University Hospital,
Nottingham

Stroke is a common disease in patients with cardiac problems and both myocardial and cerebral infarction share a common pathogenesis. As with myocardial infarction, there is now much interest in cerebral salvage after stroke, the aim being to reduce mortality and improve recovery. The trial of United Kingdom stroke treatment (TRUST) was the first British multicentre, acute intervention study on stroke and used the calcium channel blocker nimodipine, which increases cerebral blood flow and has cytoprotective properties. Seventeen centres participated in the study. Patients were entered if they were older than 40, had become hemiparetic in the previous 48 hours, were conscious, able to swallow, and had been independent before the stroke. Those entered received nimodipine 40 mg three times a day or matching placebo for 21 days. The primary end point was functional independence at six months, measured on an activities of daily living scale, the Barthel index. From preceding two tail power calculations 1200 patients gave greater than 90% probability at the 5% significance level of detecting a 10% difference in the proportions of patients independent with each treatment. In all 4507 patients were assessed, of whom 1215 (27%) were entered. The age of patients ranged from 35 to 97 (mean 73) years. A total of 607 received nimodipine and 608 placebo, the two groups being well matched in terms of preceding fitness and stroke severity. By six months 55% of the nimodipine and 58% of the placebo group were independent, the odds ratio for independence with nimodipine being 0·88 (95% confidence interval 0·7 to 1·1). For mortality the odds ratio with nimodipine was 1·22 (0·95 to 1·57). Activities of daily living and neurological scores also suggested delayed recovery in the nimodipine group at three weeks.

This study showed no evidence of a beneficial effect from nimodipine when administered within 48 hours of stroke onset. However, it does show that the lessons learnt from trials in myocardial infarction have now been translated into trials of acute teatment in stroke. TRUST was the first of such large, pragmatic studies and the next decade will see many more such trials, including thrombolysis in stroke.

Br Heart J 1991;66:114–6

LETTERS TO THE EDITOR

- *The British Heart Journal welcomes letters commenting on papers that it has published within the past six months.*
- *All letters must be typed with double spacing and signed by all authors.*
- *No letter should be more than 600 words.*
- *In general, no letter should contain more than six references (also typed with double spacing).*

Prevalence of coronary heart disease

SIR,—In the November 1990 issue of the *British Heart Journal* you published our paper "Prevalence of coronary heart disease in Scotland: Scottish Heart Health Study" (1990;64:295–8) with an editorial "Getting a handle on the prevalence of coronary heart disease" (1990;64:291–2). While we were pleased to see the former in print, and the editorial draws attention to the paper and begins reasonably favourably, comments and statements appearing towards the end have given offence.

The editorial inaccurately states that in the published article we "go beyond . important observation to imply that these methods can be relied upon to support the view that coronary heart disease is more prevalent in women than in men". We do no such thing. We contrast the correlations between the different measures of prevalence and mortality *within* the two sexes, including the Rose angina questionnaire. The latter shows a higher prevalence of mild chest pain in women than in men, not an original observation. We point out that this measure correlates better with mortality from coronary heart disease than do the others, particularly in women, "despite the lower specificity of angina for coronary heart disease in women"—hardly a claim that "these methods can be relied upon". Both cardiologists and epidemiologists know that angina pectoris is not pathognomonic of coronary heart disease, even where coronary heart disease is common, and its specificity (and hence false positives) vary by age and sex.

The editorial questions whether the Rose questionnaire is too lacking in sensitivity and specificity to be applied to "smaller groups" such as "Scottish districts". The smallest district studied had a total population of 35 000 and the largest 435 000 while the mean and median were between 120 and 150 000. We rejected most small districts from the study because of the instability of their mortality rates, and not because of possible statistical problems with surveys. With the exception of the two MONICA districts the number of men and women surveyed was approximately the same in each district—450. The confidence intervals for estimates of frequencies are related to the size of the random sample taken, and are independent of the size of the population sampled. They are similar for Roxburgh, population 35 000 and for South Glasgow, population 325 000

There are problems too with the disparaging contrast of measures of prevalence with "the 'hard' data for rates of hospital admission for infarction". Were routine statistics on hospital discharges as "hard" as all that, we in Dundee would not have had to commit as much time and effort as we have to their validation, with colleagues in Glasgow, in the Scottish and World Health Organisation MONICA studies, and we would not have been designated as a WHO Quality Control Centre and Collaborating Centre in cardiovascular epidemiology for training and methodology in this area. Equivalent validation work is also being done in the USA in the ARIC study.

The penultimate paragraph appears to be suggesting that we are accusing physicians of systematic misdiagnosis, and then goes on "It is irresponsible for epidemiologists to present incomplete and not fully developed observations and theories because publication of such ideas in a clinical journal implies that they should be incorporated into clinical practice." Even out of context the statement is extraordinary if you analyse it. What are referees and editors responsible for? Where is the epidemiologist, or the clinician, who thinks that epidemiological survey methods are both necessary and sufficient for clinical diagnosis of surgical disease?

There is nothing incomplete or undeveloped about either the theoretical basis of the paper or the observations. The findings were presented to the International Epidemiological Association in Helsinki in 1987 and to the European Congress of Cardiology in Vienna in 1988, to critical acclaim, before submission to the *British Heart Journal* in 1989. The question to which we addressed ourselves (like much of epidemiology) is relevant to clinicians. Variations in coronary heart disease mortality could correlate with morbidity (and therefore the need for clinical services) or with sudden cardiac death alone, largely inaccessible to clinicians. That mortality and morbidity do indeed correlate is of great importance to clinicians in areas of high coronary heart disease mortality whose resources are not commensurate. Clinicians frequently leap across from mortality rates to the need for clinical services. In this case an epidemiological study has provided essential stepping stones

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We apologise for inadvertent offence caused to the authors by the editorial If an implication could have been drawn that the authors were attempting to apply epidemiological methods to clinical practice, we know this not to be so.—ED *British Heart Journal*

Cardiac catheterisation with 5 French catheters

SIR,—I should like to comment on the article by O'Sullivan *et al* (*British Heart Journal* 1990;64·211–3). They cited a recent paper by Kohli *et al* in which the quality of coronary angiograms obtained with 5F and 7F catheters was compared in the same group of patients.[1] These workers concluded that "the conventional 7F coronary catheter appears to be superior to the 5F catheter in regard to diagnostic accuracy and image quality because of the higher flow rate possible with the former, allowing greater coronary filling. Also, while high flow may be possible in 5F catheters, thinner outer walls may compromise torque . . . However, in view of the frequent incidence of non-diagnostic angiograms in patients using 5F catheters, angiographers must be aware that in some patients it may be necessary to up size to larger bore catheters to achieve adequate angiographic results . . ." Brown and MacDonald reviewed 100 cases in which 5F catheters were used and encountered such a major problem of engagement and stability in the right coronary artery with the Judkins curve that they abandoned it after their first six cases and used a modified right coronary Amplatz catheter.[2] These workers, however, thought the 5F catheters were as easy to manipulate as bigger catheters They also had difficulty in entering the left ventricle with a pigtail catheter until they changed their technique With these modifications they thought the 5F catheters were satisfactory and have continued to use them as standard for day case catheterisation.

Molajo *et al* conducted a formal prospective randomised comparison of 5F super-flow and conventional 8F catheters in 34 patients.[3] They concluded "that the 8F catheter is more manoeuvrable and thus reduces x-ray dose received by both patient and investigator. Furthermore, the super-flow (5F) catheter neither reduced the time to achieve haemostasis after catheterisation, nor the incidence of bruising. It produced poor quality left ventriculograms"

As recently as June 1990, in a study of early ambulation after coronary arteriography, Kern *et al* used special large lumen 5F catheters to overcome these previously noted problems and obtained a 92% success rate for coronary opacification with a limited range of catheter shapes and seemingly without loss of angiographic quality.[4] They did not experience diminished torque control with their catheters.

In view of the differences of opinion in published reports we need a proper randomised study to compare the latest 5F catheters with traditional 7F catheters.

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1 Kohli RS, Vetrovec GW, Lewis SA, Cole S Study of the performance of 5F and 7F catheters in coronary angiography a functional comparison *Cathet Cardiovasc Diagn* 1989,18 131–5.
2 Brown RI, MacDonald AC Use of 5F catheters for cardiac catheterisation and coronary angiography, a critical review *Cathet Cardiovasc Diagn* 1987;13 214–7.
3 Molajo AO, Ward C, Bray CL, Dobson D. Comparison of the performance of super-flow (5F) and conventional 8F catheters for cardiac catheterisation by femoral route. *Cathet Cardiovasc Diagn* 1987;13 275–6
4 Kern MJ, Cohen M, Talley JD, *et al* Early ambulation after 5 French diagnostic cardiac catheterisation results of a multicentre trial *J Am Coll Cardiol* 1990,15:1475–83

A controlled trial of community based coronary rehabilitation

SIR,—We read with interest the excellent study of Bethell and Mullee (1990;64:370–5). In a large randomised controlled trial they showed both the safety and the benefits of a coronary rehabilitation programme after infarction which included exercise training three times a week for three months.

As an index of physical fitness or of exercise capacity Bethell and Mullee estimated peak oxygen consumption ($\dot{V}o_2$max) using the Astrand-Ryhming nomogram. Though the

$\dot{V}o_2$max recorded during a progressive maximal exercise test is a reliable index of exercise capacity,[1] there are methodological difficulties with the prediction of $\dot{V}o_2$max when the Astrand-Ryhming nomogram is used. This nomogram is based upon extrapolation from paired observations of heart rate and either oxygen uptake or (as in the present study) external work rate during a submaximal test. Unfortunately the predicted $\dot{V}o_2$max may differ widely from the actual $\dot{V}o_2$max, the standard error of the estimate being some 15%.[2] Furthermore, the original nomogram was based on data from young healthy students of physical education,[3] and may not be applicable to older subjects or to those with cardiac disease. Astrand himself and other authors have recently discussed the limitations of the nomogram.[2,4] Finally, the effect of physical training in the present study may have been to improve cycling efficiency, which by altering the relation between external work rate and oxygen uptake would lead to artificially high values of predicted $\dot{V}o_2$max.

Rather than extrapolate data to predict $\dot{V}o_2$max, the submaximal data themselves could be used. For example, in the study by Bethell and Mullee, a standardised measurement of heart rate at a given work rate may have been a more appropriate way of assessing exercise capacity. Despite reservations about the Astrand-Ryhming nomogram there is no doubt that Bethell and Mullee have shown valuable improvements in their patients after rehabilitation both in general well-being and in the rate-pressure double product at submaximal work rates.

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1 Astrand P-O, Rodahl K. *Textbook of work physiology* 3rd ed. New York: McGraw-Hill, 1986:299–304.
2 Astrand P-O, Rodahl K. *Textbook of work physiology*. 3rd ed. New York McGraw-Hill, 1986:376
3 Astrand P-O, Ryhming I. A nomogram for calculation of aerobic capacity (physical fitness) from pulse rate during submaximal work. *J Appl Physiol* 1954;7·218–21.
4 Legge BJ, Banister EW The Astrand-Ryhming nomogram revisited. *J Appl Physiol* 1986; 61 1203–9.

This letter was shown to the authors who reply as follows:

Sir,—We thank Dr Davies and Dr Greig for their kind comments.

We agree that there are problems with using the Astrand-Ryhming nomogram to measure $\dot{V}o_2$max (though we were less aware of this in 1979 when the trial was conceived). Nevertheless, changes in the $\dot{V}o_2$max as predicted from this test do reflect proportional changes in physical fitness.

A small part of the apparent increase in fitness of the treatment group *may* have come from improved cycling efficiency. Unfortunately a standardised measurement of heart rate at a given work rate would have been subject to the same error.

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BOOK REVIEW

An Era in Cardiovascular Medicine. Edited by Suzanne B Knoebel and Simon Dack (Pp xiv + 330; $59.50.) New York, Amsterdam, and London: Elsevier Science Publishing Company, 1991. ISBN 0-444-01580-9.

During 1989 the American College of Cardiology celebrated the fortieth anniversary of its founding. From a nucleus of cardiologists based in New York it has grown into an influential organisation with members in all parts of the world and international influence largely, but by no means exclusively, exerted through two major activities—its annual scientific sessions and the *Journal of the American College of Cardiology*. The journal and its predecessor must be unique in that they have had a single editor, Simon Dack, since the college first started its own journal in 1958. One of the ways in which the college celebrated its anniversary was to invite Suzanne Knoebel of Indianapolis, as guest editor, to produce a series of scientific papers to appear each month in the journal. These have now been gathered together in a volume, supplemented by original material and two valuable commentaries.

Each chapter can stand on its own and reflects expert views on diseases, techniques of diagnosis and treatment, pathology, molecular biology, and decision making—a wide range of topics of current concern. Each is dealt with in an individual fashion and reflects the approach, experience, and quirks of an author or small team. Arrhythmias exemplify this well. Borys Surawicz illuminates the difficulties in finding medications for ventricular arrhythmias; Wellens and Brugada concisely take this further and explore the whole range of treatments for arrhythmias in general; and Richard Cohen and his group remind us of the mathematical concepts that may underlie the physiological and pathological expressions in these disorders. This links very well with Charles Fisch's chapter on the evolution of the electrocardiogram which itself, of course, has wider implications directly relevant to many other chapters.

One could go on and on listing and analysing contributors and contributions but that would only distract from the important message—that this is a book well worth reading and an essential source of up to date information. Various other groupings easily come to mind. Two important additional chapters do, however, orientate the reader, and the respective authors raise important issues. Eugene Braunwald writes lucidly of the golden age of cardiology encompassed by the era commemorated; and in a concluding chapter Sylvan Weinberg, editor of the college's influential audiotape journal *ACCEL*, expresses the clinician's point of view and compares current issues with those that dominated the scene in 1949, reminding us of the emphasis in that year as seen in the pages of the only two English language cardiological journals then published, the *American Heart Journal* and the *British Heart Journal*. The comments by these distinguished educators put in perspective the topical and authoritative contributions that cover the spectrum of cardiology so helpfully This expanded version of the symposium is a great credit to the editorial selection and presentation undertaken by Dr Knoebel and Dr Dack.

DENNIS M KRIKLER

The title reviewed here is available from the BMJ Bookshop, PO Box 295, London WC1H 9TE. Prices include postage in the UK and for members of the British Forces Overseas, but overseas customers should add £2 per item for postage and packing Payment can be made by cheque in sterling drawn on a UK bank, or by credit card (MasterCard, VISA, or American Express) stating card number, expiry date, and your full name.

BRITISH CARDIAC SOCIETY NEWSLETTER

The annual meeting of the society in Glasgow had a larger attendance than for any we have had previously. The total (excluding exhibitors) was 1266. Of these, 766 were physicians or surgeons, 400 were nurses, and 150 were technicians. The venue proved to be popular. The programme met with general approval; the facilities within the conference centre were generally excellent The proximity of the exhibition kept people together, and saved valuable time during breaks in the programme; and the convenience of an adjoining hotel was an advantage that will be missed when we return to Wembley. The success of the meeting is a tribute to Ian Hutton and his colleagues, who took much of the burden of preparation, and ensured that we enjoyed something of the ambience of the "city of culture".

When we consider we have had the perfect meeting, we can relax our efforts. That has not happened, nor of course will it. Even Glasgow had its blemishes. The numbers who will be attracted by particular topics cannot always be predicted; thus some sessions required a larger hall than was allocated and were overcrowded. Signposting for the break out meetings within the hotel was judged inadequate, especially on the first day when the layout was unfamiliar. The standard of slides was not uniformly good. Colour seems sometimes to be a substitute for careful composition rather than an aid to clarity Colour used judiciously can enhance a presentation, but a few speakers do themselves less than justice with psychedelic displays of overcrowded data Whatever happened to the old guideline of not more than seven words to a line or five lines to a slide? Posters remain a problem. They form an integral part of the scientific meeting and many subjects lend themselves better to this form of exposure than to spoken presentations. In Glasgow, the posters may have been set too closely together. Some authors seemed diffident about discussing their content, or perhaps those of us who were viewing the posters did too little to initiate debate.

Interest is at too low a level, and so the formula is not yet correct. New ideas are being debated. We will let you know the outcome, but more experiments are needed. Meanwhile, we welcome your views.

One of the disadvantages of travelling a long way for a meeting is the extra expense The society awards travelling scholarships to help overcome this problem, with priority given to those in training grades and to those who are presenting papers or posters. Even now many of our younger cardiologists seem unaware of this opportunity. Up to 25 travel grants of £400 will be available for the European meeting in Amsterdam (forms to be returned by 11 July), and 40 grants of £150 will be made when the society visits Harrogate next year. Cost has to be a consideration. none of us welcomes spending large sums of money to attend meetings, even those who can undoubtedly afford to do so. It was salutary to have been sitting next to a visitor from an eastern European country at a recent meeting in Montreal on disaster medicine. He had spent almost eight months salary to attend. Perhaps we have too many meetings so that we do not value them quite to this degree?

Does the society contribute enough to the campaign against smoking? We are a non-smoking society, but that in itself may not make the tobacco industry tremble. Some—particularly the ex-smokers among us—have a certain proselytising zeal The industry may even survive that. We write each year to offer advice to the Chancellor of the Exchequer on taxation policy, but he may not always pay close attention to our wisdom, and the industry continues to prosper. But now more: the British Thoracic Society has taken the initiative in organising a combined approach by medical colleges and associations to launch a campaign to reduce smoking It has the specific aim of putting pressure on the government to ban the promotion of smoking by advertising, promotion, and sponsorship. Sadly the government has been lukewarm to a similar proposal from within the European Community. We will participate in the new joint initiative Council have nominated Andrew McLeod to be our representative. The first joint meeting took place on 23 May. Perhaps the tobacco industry will now at least shudder, and we should offer no words of comfort.

The recent Annual Meeting marked the retirement from council of three members who have each contributed much to the society· Andrew Henderson, Ian Hutton, and Stewart Hunter The three replacements are Roger Hall, Andrew McLeod, and David Ward The constitution of the society permits one more member to be coopted, and this will be the President of the British Paediatric Cardiac Association. We are proposing that the constitution be amended to allow two other additions to council—the Postgraduate Cardiology Advisor (at present Howard Swanton) and the Chairman of the College Cardiology Committee (now Brian Pentecost). In the meantime, these will be invited to attend council meetings

We will soon be sending all members of the society up to date lists showing the officers, the council members, the membership of the committees, and contacts for the affiliated groups. The society has evolved in many ways in the past 12 months, and in particular we have developed a committee structure with membership selected by council. We have heard whisper that this is not sufficiently democratic But could we be equally effective with any other structure? We live in a world that seems increasingly hostile to many precepts that are needed for the continued provision of good cardiological care. We must have an organisation that can respond quickly and effectively—within the constraints of our charitable status—to challenges that come from many directions But it is not enough to be defensive. We also need a structure that will encourage improvement of established practices and the development of new ones. Inevitably, day to day decisions must be left to a few But committees are accountable to council, and council is accountable to the membership. It is understandable that such major changes arouse some anxieties, and they are important because we must maintain a strong consensus in the new paths that we tread. Perhaps we allow insufficient time for debate at our annual meeting Should we change slightly the balance in the emphasis on organisational and academic matters? We were disappointed, however, that relatively few attended the special session in Glasgow on the contentious matter of training. As always, we need the views of the society. Write to us if you believe that wide debate through the newsletter may be helpful—we are constrained by space but are not averse to contrary views . . Alternatively, write to a council member Only by continuing exchange of views can we ensure that the society does reflect the opinions and intentions of its members.

DOUGLAS CHAMBERLAIN
President, British Cardiac Society
PAUL OLDERSHAW
Secretary, British Cardiac Society
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London NW1 4LB

NOTICES

1991

An **International Conference "Look After Your Heart"** will be held in London on 19 and 20 September: Judy Berry, Conference Organiser, Look After Your Heart, Health Education Authority, Hamilton House, Mabledon Place, London WC1H 9TX (Fax: 071 387 0550; Tel: 071 383 3833).

A **Symposium on Alcohol and Cardiovascular Diseases** will be held in Scheveningen on 1 and 2 October: Ms Fl de Vrijer, Secretariat Alcohol Symposium, c/o TNO Food and Nutrition Research, PO Box 360, 3700 AJ Zeist, The Netherlands (Fax· +31 3404 57224; Tel +31 3404 44218).

1992

The **2èmes Journées Européennes de la Société Française de Cardiologie** will take place in Paris on 16 to 18 January (deadline for submission of abstracts is 15 July 1991): SFC, 15 rue de Madrid, 75008 Paris, France (Fax. (33) 1 43 87 17 14; Tel: (33) 1 43 87 95 14).

The Annual Meeting of the **British Cardiac Society** will take place at the Harrogate International Centre, on 26 to 29 May

The **XI International Symposium on "Drugs Affecting Lipid Metabolism"** will be held in Florence on 13 to 16 May: Organising Secretariat, XI DALM, Fondazione Giovanni Lorenzini, Via Monte Napoleone 23, 20121 Milan, Italy (Fax. (02) 781511, Tel· (02) 76002267–783868) and for USA: Organising Secretariat, XI DALM, Giovanni Lorenzini Medical Foundation (Fax 713 796 8853; Tel. 713 797 0401).

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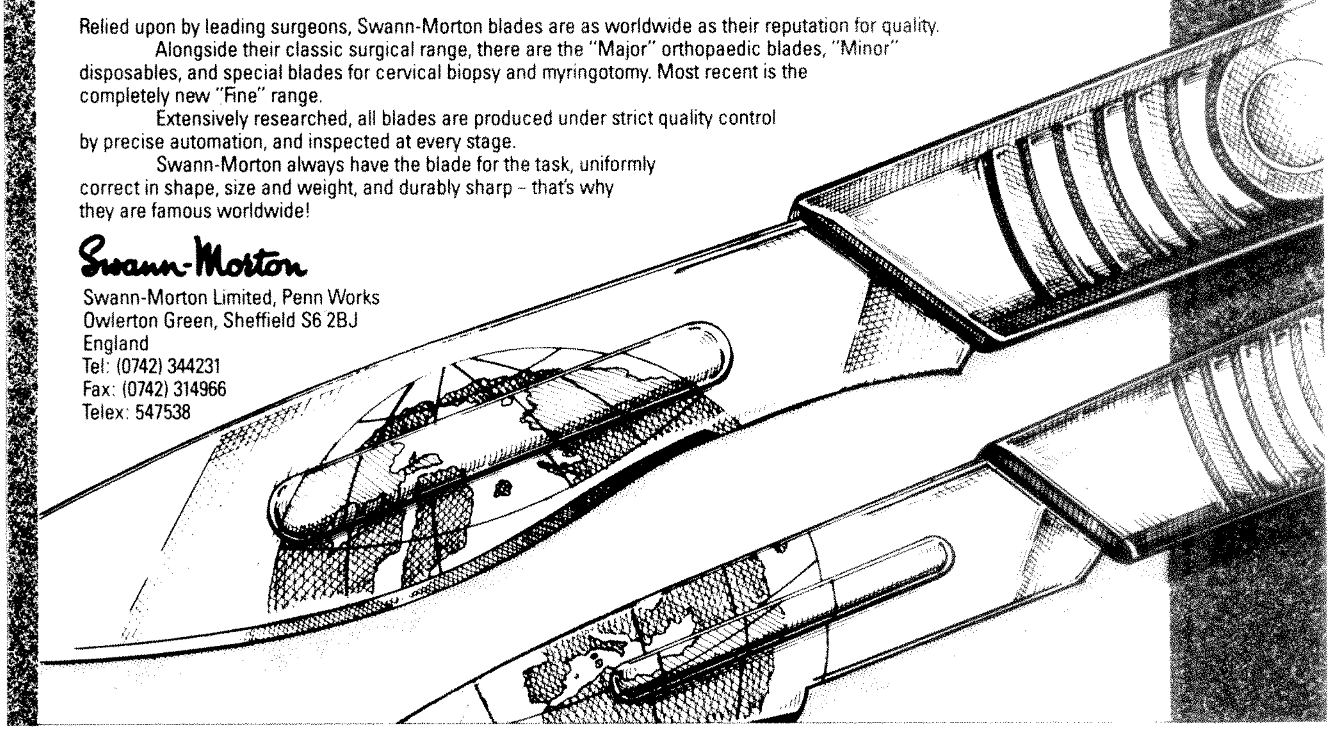

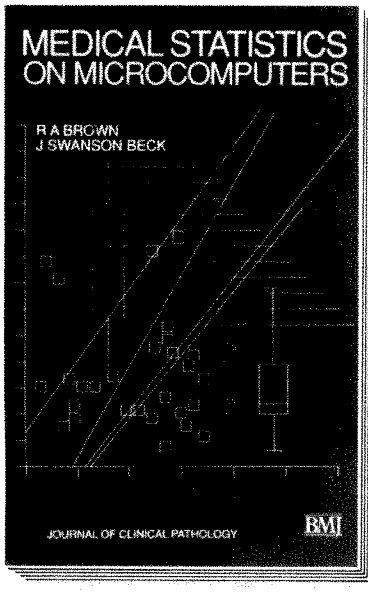
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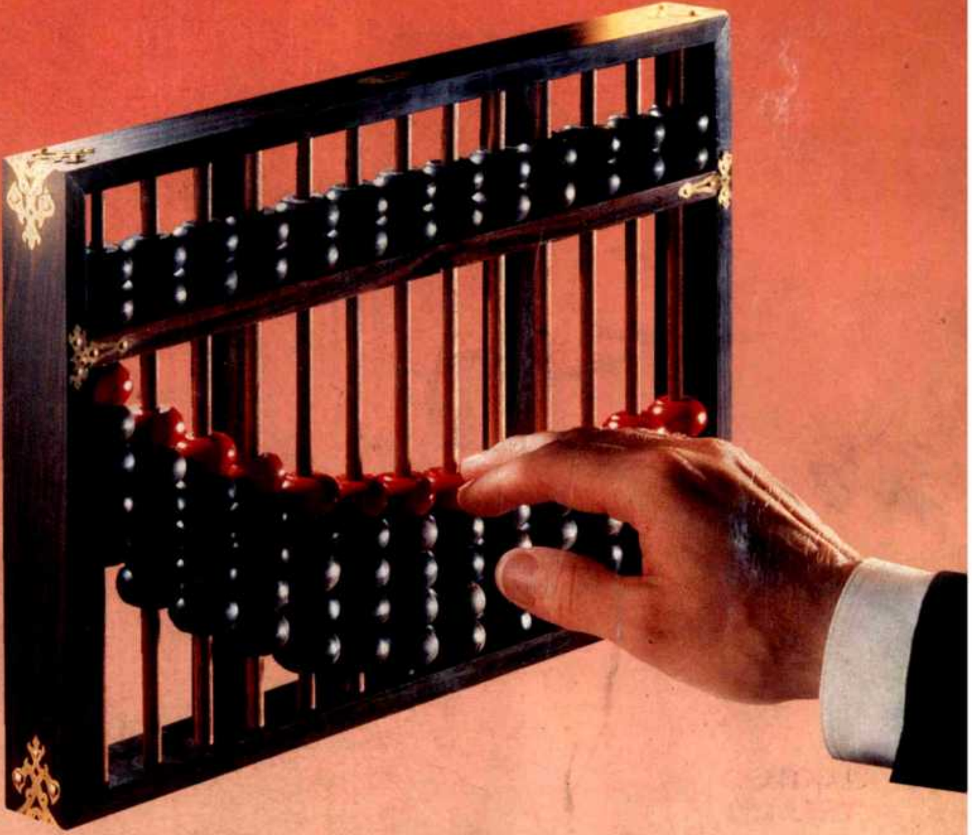

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BRITISH MEDICAL ASSOCIATION TAVISTOCK SQUARE LONDON WC1H 9JR

BRITISH HEART JOURNAL

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dy Group, *Europ. Heart J.*, 1987, **8**, 77.

id Research Clinics Programme, *J. Amer. med. Ass.*, 1984, **251**, 351-364.

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References

1. Data on file. In trials LIPOSTAT demonstrated an LDL-cholesterol reduction of up to 34% from baseline values (after 8 weeks, 40 mg nightly).

Br Heart J 1991;66:117–8

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BRITISH
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Editorial

Battery powered angioplasty

The principle of balloon angioplasty—dilatation of stenosed arteries by nothing but pressure—is so simple that doctors and patients find it quite logical. But in our high-tech environment, where lost door keys answer to a whistle and pacemakers make their own decisions and respond to questions, balloon angioplasty may appear too simple to be taken seriously. The inflation of a fluid filled angioplasty balloon with the help of an ordinary syringe does not produce noise and is often not even recognised by the somewhat distracted cath lab personnel, who are supposed to record the duration of the inflations. In contrast battery powered angioplasty makes itself known by smart looking, thoughtfully engineered electric motors with a disposable energy supply that generate a distinct noise which tells everybody nearby (including the patient) that something important is happening.

In this issue of the *British Heart Journal* two types of battery powered angioplasty are analysed by workers who used these instruments hoping to overcome some unresolved problems with percutaneous transluminal coronary angioplasty (PTCA). The paper by Anderson and Ward deals with what has been termed "slow rotational angioplasty"[1] whereas Serruys *et al* describe their initial experience with so-called "directional atherectomy".[2] Both methods use battery powered electric engines (completely disposable for directional atherectomy and reusable but more expensive for rotational angioplasty) to turn a thin drive shaft that runs through the entire length of the catheter and rotates either a blunt tip at the end or a cylindrical knife passing over a side opening. The targets are chronic occlusions (for the turning blunt tip) and atheromatous plaques (for the cutting knife). Both instruments are bulky, not cheap, and require special training for their user. The fact that they are fairly rigid and have a larger diameter than angioplasty balloons makes them potentially offensive weapons. So it seems quite legitimate to undertake a critical analysis of their merits and disadvantages, in order to decide whether such techniques are justified.

Directional atherectomy

When Simpson, an innovative angioplasty pioneer, designed his instrument he had in mind to remove the *corpus delicti* from the coronary (and peripheral) artery, hoping to reduce acute and chronic problems inherent in balloon angioplasty.[3] He was right as far as the acute problems were concerned[4] but not quite right about the chronic problems.[5] Directional atherectomy rarely produces abrupt closure of the artery, probably because its mode of action avoids the stretching and splitting of plaques and the subsequent creation of intimal plaques and dissections. The sharp, rotating knife creates a smooth cut without the customary fissures and cracks; but the stiff housing itself (despite the semiflexible distal collecting chamber) may damage the artery, in particular where there are bends to be negotiated. Experience has shown that this may account for some of the acute problems. The case of detachment (and, fortunately, successful retrieval) of the tissue container at the tip of the device described in the current issue is unique. The attachment of the container has since been altered.

For many indications the long term outcome after atherectomy has not matched initial expectations. Surprisingly, the open wound left after transluminal plaque removal is as good a basis for restenosis as the compressed and split plaque. If you take into account the relatively large vessel size of most target vessels submitted to this procedure the overall restenosis rate after atherectomy of primary lesions (23%) is not much lower than that after PTCA alone.[6] In patients who have had previous angioplasty at the same site, this figure is higher and becomes 53% for the third attempt, and when the lesion was located in the mid portion of a vein bypass graft restenosis was seen in 61%.[7]

Why is this so? Presumably there are several reasons. Even clean cuts do not produce clean vessels. Flow in normal vessels is laminar, whereas after atherectomy it is likely to be turbulent—an important risk factor for restenosis. Secondly, the deep vascular injury (up to 70% atherectomy specimens contain media and 30% contain adventitia[8,9]) may trigger an exuberant repair process. Intuitively, atherectomy would seem to lend itself beautifully to the removal of very eccentric localised lesions that can be excised with one or two precise, clean cuts. Indeed, if such cases are singled out the restenosis rate is very low and compares favourably with all other existing transluminal techniques.[10] In such patients the use of the larger guiding catheter, with its inherent problems, is certainly justified.

On page 122 Serruys *et al* report encouraging results after directional atherectomy.[2] The angiographically determined luminal diameter after this procedure was consistently better than would have been expected after balloon angioplasty. This is not surprising. In practice it should be possible to sculpture the artery to any desired result by removing as much material as is prudent. The issue therefore is not the potential for plaque removal but rather the right moment to stop before cutting through the adventitia. On the other hand, there is little correlation between the diameter stenosis after angioplasty and long term outcome. The Rotterdam data suggest a 77% uneventful six month follow up, but no angiographic data are presented. Thus the long term consequences of the promising initial outcome have yet to be demonstrated and compared with other techniques.

Other atherectomy devices

Another battery powered angioplasty device has been introduced by Stack; it is called the transluminal extraction cathether (TEC) and it aspirates the debris that the conical cutter, which is mounted at the tip of a shaft revolving at 750 rpm, produces when cutting forward through atheromatous plaques.[11] This instrument has shown its merits in extremely friable and diffusely diseased vessels where the aspiration of mobilised atheromatous material prevents downstream embolisation.[12] It does not allow, however, precise "sculpturing" of vessels and the mean residual diameter stenosis was 30%[13]; there is a relatively high overall restenosis rate of more than 40%.[13]

The "rotablator", launched by Auth and colleagues,[14 15] uses compressed air (not batteries) to drive it at 160 000–190 000 rpm; it resembles a dental drill and creates small particles, most of which do not seem to be trapped in the capillary bed.[16 17] It may be useful in very hard, subtotal non-dilatable lesions; restenosis is frequent.[18] As is the case with the TEC device, it can only create channels—admittedly smooth and round—as large as the instrument itself.

Slow rotational angioplasty

The rationale behind this technique, which was first described by Kaltenbach (another angioplasty pioneer) and Vallbracht in 1987,[19] was the assumption that a larger and rounder tip was less likely to cause dissections during recanalisation of totally occluded arteries and that a slowly turning blunt tip would find its way through total occlusions more easily. Thus a device resembling a magnum wire was created; this is rotated at a speed of up to 200 rpm by a small motor.

Apart from the reports of Kaltenbach and Vallbracht[20–22] there are few studies of slow rotational angioplasty. Kaltenbach and Vallbracht claimed a success rate of some 65% in recanalising old chronic occlusions.[23] With a preliminary re-angiography rate of 81% they found that 38% of the successful cases were improved at four months, 33% had significant restenosis, and 28% had reoccluded.[23] To achieve recanalisation of chronic occlusions it is vital to select patients with a stump that guides the catheter towards the correct lumen. Those who used the appropriate patient selection criteria reported similar results with balloon angioplasty alone; however, the use of the magnum wire technique has certainly helped to obtain these results more easily. These different techniques have not been widely evaluated; there is only one study comparing the magnum wire technique with the conventional balloon angioplasty technique, and that was performed by the group which devised the magnum wire.[24]

Slow rotational angioplasty is not radically different from mechanical recanalisation with other devices. There is certainly an added risk when an operator uses instruments that reduce "feel", as does slow rotational angioplasty. The risks of the method are clearly shown in the paper by Anderson and Ward on page 130.[1] We should be cautious, not only about the use of this device but also about the potential risk of supposedly harmless attempts at recanalising chronically occluded coronary arteries.[25] Operators attempting this should use a familiar instrument that allows optimal tactile feedback rather than an engine driven shaft.

ULRICH SIGWART
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1 Anderson MH, Ward DE Early experience with low speed rotational angioplasty. *Br Heart J* 1991,66 130–3
2 Serruys PW, Umans VAWM, Strauss BH, *et al.* Quantitative angiography after directional coronary atherectomy. *Br Heart J* 1991;66.122–9
3 Simpson JB, Johnson DE, Thaplıyal HV, *et al* Transluminal atherectomy. a new approach to the treatment of atherosclerotic vascular disease [abstract]. *Circulation* 1985;72(suppl III):111–146.
4 Popma JJ, Topol EJ, Pinkerton CA, *et al*, for the U S. Directional Coronary Atherectomy Study Group. Abrupt closure following directional coronary atherectomy: clinical, angiographic and procedural outcome [abstract]. *J Am Coll Cardiol* 1991;17 23A.
5 Simpson J, Rowe M, Robertson G, *et al.* Directional coronary atherectomy: success and complication rates and outcome predictors [abstract]. *J Am Coll Cardiol* 1990;15:196A.
6 Simpson JB, Hinohara T, Selmon M, *et al.* Comparison of early and recent experience in percutaneous coronary atherectomy [abstract] *J Am Coll Cardiol* 1939,13:109A
7 Hinohara T, Rowe M, Sipperly ME, *et al.* Restenosis following directional coronary atherectomy of native coronary arteries [abstract] *J Am Coll Cardiol* 1990,15.196A.
8 Saflan RD, Gelbfish JS, Erny RE, *et al* Coronary atherectomy: clinical, angiographic, and histologic findings and observations regarding potential mechanism *Circulation* 1990;82.69–79.
9 Garrat KN, Holmes DR, Bell MR, *et al* Restenosis after directional coronary atherectomy differences between primary atheromatous and restenosis lesions and influence of subintimal tissue resection. *J Am Coll Cardiol* 1990;16.1665–71.
10 Simpson JB. Baim DS, Hinohara T, *et al* Restenosis of de novo lesions in native coronary arteries following directional coronary atherectomy: multicentre experience [abstract]. *J Am Coll Cardiol* 1991;17:346A.
11 Stack RS, Quigley PJ, Sketch MH, *et al.* Extraction atherectomy In· Topol EJ, ed. *Textbook of interventional cardiology*. Philadelphia: W B Saunders, 1990:363–94.
12 Stack RS, Phillips HR, Quigley PJ, *et al* Multicentre registry of coronary atherectomy using the transluminal extraction-endarterectomy catheter [abstract]. *J Am Coll Cardiol* 1990;15:196A
13 Sketch MH, O'Neill WW, Galichia JP, *et al* The Duke multicentre coronary transluminal extractio-endarterectomy registry. acute and chronic results [abstract]. *J Am Coll Cardiol* 1991,17:31A
14 Hansen DD, Auth DC, Vrocko R, *et al* Rotational atherectomy in atherosclerotic rabbit iliac arteries *Am Heart J* 1988,115 160–5.
15 Hansen DD, Auth DC, Hall M, *et al.* Rotational endarterectomy in normal canine coronary arteries Preliminary report. *J Am Coll Cardiol* 1988;11: 1073–7
16 Zacca N, Heibig J, Harris S, *et al* Percutaneous coronary high speed rotational atherectomy. new, but how safe? [abstract] *J Am Coll Cardiol* 1990;15· 58A
17 Teirstein PS, Ginsburg R, Warth DC, *et al.* Complications of human coronary rotoblation [abstract] *J Am Coll Cardiol* 1990,15:57A.
18 Niazi KA, Brodsky M, Friedman HZ, *et al.* Restenosis after successful mechanical rotary atherectomy with the Auth Rotablator [abstract]. *J Am Coll Cardiol* 1990,15:57A
19 Kaltenbach M, Vallbracht C. Rotationsangioplastik-ein neues Katheterverfahren für die nicht-operative Gefasseroffnung. *Fortschr Med* 1987; 112·842–4.
20 Kaltenbach M, Vallbracht C. Reopening of chronic coronary artery occlusions by low speed rotational angioplasty. *J Intervent Cardiol* 1989, 2.137–45.
21 Kaltenbach M, Vallbracht C. Low speed rotational angioplasty in chronic coronary artery obstructions [abstract]. *Circulation* 1989;80 (suppl II)·273.
22 Kaltenbach M, Vallbracht C, Kober G Medium-term results after reopening chronic coronary artery obstructions by low speed rotational angioplasty [abstract] *Circulation* 1989,80(suppl II) 257
23 Vallbracht C, Kaltenbach M Wiedereroffnung chronischer Arterienverschlusse [abstract]. *Z Kardiol* 1991;80 525
24 Meier B, Urban P, Villavicencio R, *et al* Magnun/Magnarail versus conventional systems for recanalisation of chronic total coronary occlusions—a randomised comparison [abstract 2693]. *Circulation* 1990,82 (suppl III).678
25 Stewart JT, Williams MG, Mulcahy D, *et al.* Myth of the "safe procedure": disobliteration of chronically occluded coronary arteries [abstract] *Br Heart J* 1991,66·43.

Br Heart J 1991,66:119–21

Editorial

The treatment of primary pulmonary hypertension

Primary pulmonary hypertension caused by narrowing of the small resistance arteries, well described by Wood,[1] is usually taken to indicate the absence of a cardiac or respiratory cause for the condition.[2,3] When the major pulmonary arteries are obstructed the disorder is often called "chronic thromboembolic pulmonary hypertension" although a history of pulmonary embolism is rare and most of these cases probably result from a previous pulmonary arteritis sometimes associated with systemic arteritis in the so-called Takayasu syndrome.[4] Post-capillary pulmonary hypertension caused by obliteration of pulmonary veins and venules (pulmonary veno-occlusive disease), is rare and rapidly fatal especially in children and young people.[5] It closely resembles pre-capillary primary pulmonary hypertension from which it can sometimes be distinguished clinically if the lung fields show small patches of interstitial oedema or a cloudy background or pulmonary arteriography shows an abnormal venous phase.

Causes of primary pulmonary hypertension

Primary pulmonary hypertension can be a complication of systemic lupus,[6,7] scleroderma,[8] CREST syndrome,[9] and mixed connective tissue disease[10] and in patients without such features there is often a hint of an autoimmune origin in the form of Raynaud's phenomenon,[11] thrombocytopenia, or a history of uveitis. Rare patients with pulmonary veno-occlusive disease have vasculitic skin lesions, which also suggest a possible immunological basis, but the origin of the disease remains obscure.[12]

Wood first suggested that primary type pulmonary hypertension had a vasoconstrictive basis. He showed that pulmonary artery pressure was reduced in patients with mitral valve disease after intravenous aminophylline and tolazoline and the intra-pulmonary infusion of acetylcholine.[13,14] The pathological features that were also thought to indicate a vasoconstrictive aetiology were hypertrophy of the media of small muscular arteries and extension of muscle into pulmonary arterioles together with dilatation (plexiform) lesions.[11] These studies showed that a few patients had a thrombotic arteriopathy which at the time was believed to have resulted from chronic microthromboembolism—though there was no evidence for this.[11] In further work, the two histological types, thrombotic and plexiform, were again separated and it was suggested that the thrombotic form might represent thrombosis in situ, possibly as a consequence of a small vessel arteritis.[15,16] Open lung biopsy has not been much used in the United Kingdom because of its failure to influence therapeutic strategies: but it was part of the protocol in the American Primary Pulmonary Hypertension Registry, which was notable for the high complication rate of biopsy in these patients. The course of the thrombotic form, which affects both male and female patients, was sometimes prolonged; plexiform arteriopathy was almost exclusively confined to young female patients.[17]

Current knowledge

Any rigid distinction between two histological types was found to be unsound in a recent study of familial primary pulmonary hypertension in which both thrombotic and plexiform lesions were found within patients and among the affected families.[18] Both types of lesion were also found in pulmonary hypertension associated with the Eisenmenger syndrome,[19] collagen vascular diseases,[6–10] in drug induced pulmonary hypertension in the aminorex fumarate epidemic,[20] in the toxic oil syndrome,[21] and associated with cirrhosis.[22]

A high frequency of plexiform lesions does seem to be associated with a more rapidly fatal course[17] and fibroblast migration through defects in the inner elastic lamina, probably the result of endothelial interruption, may herald prodromal lesions.[23] In addition, it has been suggested that the pulmonary vascular bed maintains its low resistance through the action of endothelium derived relaxation factor with plexiform arteriopathy resulting from the failure of the production or release of this factor; vasodilatation by acetylcholine (in its endothelium dependent role) has been cited as parallel evidence for this effect.[16] Endothelial cell injury as seen in rats after crotalaria ingestion,[24] or immune-mediated damage of the endothelium, as in collagen vascular disease,[25] may be responsible for myofibroblast migration and proliferation, which would explain the development of the thickening of the medial coat[16] rather than vasoconstriction. These effects or the advanced stage of the disease when patients are first seen may explain the frequently disappointing response to treatment with vasodilators, which has been the only available medical treatment apart from anticoagulants.[26] The use of anticoagulants was associated with an apparent improvement in survival in a large retrospective study that did not distinguish between subgroups.[27] It is possible that long term anticoagulants may reduce the incidence of thrombosis in situ or reduce thromboembolism secondary to the low cardiac output.[26]

Treatment with vasodilators

The association with Raynaud's disease and rare reports of regression lent support to the theory of vasoconstriction and to the extensive use of vasodilators.[13,14,28–49] None the less, vasodilators given acutely may be dangerous if they cause only systemic and not pulmonary vasodilatation.[26,36] They may be helpful if a fall in pulmonary vascular resistance allows right and thus left ventricular output to increase. Most vasodilators predominantly affect the systemic resistance vessels and will only be tolerated in patients with pulmonary hypertension if there is a sufficient effect also on the pulmonary vessels to permit the cardiac output to rise and maintain blood pressure. Virtually every vasodilator has been tried and the results published. Though nifedipine has found most favour,[31,37,38] it too is not without its disastrous side effects. This is because its depressant effect on myocardial contractile force may be unmasked and this can cause circulatory collapse if the right ventricular afterload is not reduced.

Acute testing of vasodilators has been used to predict benefit and prevent untoward reactions.[43,47,49] These studies have shown that those patients who are capable of responding tend to respond to whatever vasodilator is given—a favourable response to prostacyclin was associated with a good response to nifedipine also.[47] So long term infusions of prostacyclin into the pulmonary artery, a treatment that is highly demanding of both patient and doctor and not without complications,[45] is not justified. Most patients will not tolerate high doses of calcium channel blocking drugs but remarkable reductions in pulmonary artery pressure and resistance were achieved in some patients treated with high doses of diltiazem or nifedipine and the improvement was sustained over months.[46] These successes and rare cases of spontaneous improvement[50 51] have sustained the use of these usually unsuccessful and poorly tolerated agents.[52]

Outcome

All of the studies have shown a wide variation in survival, from months up to 30 or even 40 years from diagnosis.[27 44] This has been used as evidence for diverse aetiologies but it could equally well result from the same cause having disastrous consequences, as in some young females who show major vascular consequences and a mainly plexiform arteriopathy, or a more stable protracted course in patients with the less severe changes of a mainly thrombotic arteriopathy. Both could result from a vasculitic illness. Studies of the natural history of the disease showed that the sickest patients survived the shortest time. Right ventricular failure is the single most important determinant of prognosis.[44] This has been recorded in published reports which detailed a right atrial pressure > 6 mm Hg, a stroke volume index of < 22 ml/m^2, a cardiac index $< 2{\cdot}8$ l/min/m^2, or a pulmonary artery saturation $< 63\%$ as adverse prognostic features[27 53–55] but did not emphasise right ventricular failure as such. Not surprisingly, the pulmonary artery pressure is usually not a determinant because it fails to rise once the output starts to fall as the right ventricle fails.

More recent work has used echocardiography to measure these indices[56] and it may be more informative than catheterisation in showing right ventricular function and pressure serially, tricuspid regurgitation, and when right ventricular systolic or diastolic pressure is higher than the systemic pressure. A low cardiac output, abnormal tricuspid Doppler diastolic filling patterns due to prolonged isovolumic relaxation, tachycardia, and curtailed right ventricular filling time may also be found.

These omens of poor or deteriorating right ventricular function indicate a short life expectancy in patients with primary type pulmonary hypertension; most of these patients do not survive three years from the time of presentation. At present, heart/lung transplantation offers the only hope of longer term survival with restoration of their quality of life. Improved management of rejection and infection with newer drugs and routine bronchoscopic surveillance to detect these complications early has resulted in much better survival. Three year survival is now 65% and the incidence of obliterative bronchiolitis is lower.[57] These patients with primary type pulmonary hypertension who have no disease elsewhere and who are young and otherwise fit are most likely to benefit from this procedure. Moreover, their hearts can be used in recipients with pulmonary hypertension complicating left heart failure.

The future

Future treatments are likely to arise as developments in vascular and cell biology lead to a better understanding of the growth factors that determine the proliferative responses to endothelial injury.[58] Future understanding of adhesion molecules such as fibronectin and von Willebrand factor which influence cell migration and proliferation,[59] of charge related microvascular injury,[60] and vascular remodelling after injury[61] may lead to more successful treatments. These may be particularly relevant if primary type pulmonary hypertension follows a pulmonary vasculitis which, if it is not rapidly fatal, can achieve haemodynamic stability. It is unfortunate that delayed initial presentation may still inhibit the use of potentially successful agents. It seems that we are a long way from being able to treat primary type pulmonary hypertension effectively because of the late presentation of most of the patients. Only the fortunate few, in spite of or because of our management, will show stability or improvement. For most of them heart/lung or single lung transplantation is likely to remain the best available treatment.

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1 Wood P. Pulmonary hypertension *Br Med Bull* 1952,8 348–53
2 Hughes JD, Rubin LJ Primary pulmonary hypertension. *Medicine (Baltimore)* 1986;65:56–72.
3 Rich S. Primary pulmonary hypertension *Prog Cardiovasc Dis* 1988;31: 205–38.
4 Kawai C, Ishikana K, Kato M, *et al* "Pulmonary pulseless disease": pulmonary involvement in so-called Takayasu's disease *Chest* 1978;73: 651–7.
5 Thadani U, Burrow C, Whitaker W, *et al* Pulmonary veno-occlusive disease *QJ Med* 1975,44 133–59.
6 Wakaki K, Koizumi F, Fukase M. Vascular lesions in systemic lupus erythematosus with primary pulmonary hypertension. *Acta Pathol Jpn* 1984,34 593–604
7 Asherson RA, Oakley CM. Pulmonary hypertension and systemic lupus erythematosus *J Rheumatol* 1986;13 1–5.
8 Young RH, Mark GJ Pulmonary vascular changes in scleroderma. *Am J Med* 1973,64 998–1004
9 Salerni R, Rodnan GP, Leon DF, *et al.* Pulmonary hypertension in the CREST syndrome variant of progressive systemic sclerosis (scleroderma). *Acta Intern Med* 1977,86.394–9
10 Sullivan WD, Hurst DJ, Harmon CE, *et al* A prospective evaluation emphasizing pulmonary involvement in patients with mixed connective tissue disease. *Medicine (Baltimore)* 1984,63 92–107
11 Wagenvoort CA, Wagenvoort N. Primary pulmonary hypertension. a pathologic study of the lung vessels in 156 clinically diagnosed cases. *Circulation* 1970;42 1163–84.
12 Sanderson JE, Spiro SG, Hendry AT, Turner-Warwick M. A case of pulmonary veno-occlusive disease responding to treatment with azathioprine. *Thorax* 1977;32·140–8
13 Wood P. The vasoconstrictive factor in pulmonary hypertension. In· Adams WR, Veith I, eds. *Pulmonary circulation* New York Grune and Stratton, 1959.294–301
14 Wood P. Pulmonary hypertension with special reference to the vasoconstrictive factor *Br Heart J* 1958;20:557–70.
15 Bjornsson J, Edwards WD Primary pulmonary hypertension a histologic study of 80 cases *Mayo Clin Proc* 1985;60 16–25
16 Rich S, Brundage B. Pulmonary hypertension. a cellular basis for understanding the pathophysiology and treatment. *J Am Coll Cardiol* 1989;14: 545–50.
17 Pietra GG, Edwards WD, Kay M, *et al* Histopathology of primary pulmonary hypertension A qualitative and quantitative study of pulmonary blood vessels from 58 patients in the National Heart, Lung, and Blood Institute, Primary Pulmonary Hypertension Registry. *Circulation* 1989,80·1198–206.
18 Loyd JE, Atkinson JB, Pietra GG, Virmani R, Newman JH. Heterogeneity of pathologic lesions in familial primary pulmonary hypertension *Am Rev Respir Dis* 1988;138 952–7.
19 Heath D, Edwards JE. The pathology of hypertensive pulmonary vascular disease: a description of six grades of structural changes in the pulmonary arteries with special references to congenital cardiac septal defects. *Circulation* 1958,18:533–47
20 Gurtner HP Aminorex and pulmonary hypertension *Cor Vasa* 1985,27:160–71.
21 Gomez-Sanchez MA, Mestre de Juan M, Gomez-Pajuelo C, Lopez JI, Diaz de Atauri M, Martinez-Tello FJ Pulmonary hypertension due to toxic oil syndrome. A clinicopathologic study. *Chest* 1989;95·325–31.
22 Morrison EB, Gaffrey FA, Eigenbrodt EH, Reynolds RC, Buja LM Severe pulmonary hypertension associated with macronodular (post-necrotic) cirrhosis and auto-immune phenomena *Am J Med* 1980;69:513–9.
23 Heath D, Smith P, Gosney J, *et al.* The pathology of the early and late stages of primary pulmonary hypertension *Br Heart J* 1987,58 204–13
24 Hislop A, Reid L Arterial changes in Crotolaria Spectabilis-induced pulmonary hypertension in rats *Br J Exp Pathol* 1974,55:153–7.
25 Rich S, Kieras K, Hart K, *et al.* Antinuclear antibodies in primary pulmonary hypertension *J Am Coll Cardiol* 1986,8·1307–11.
26 Oakley CM. Management of primary pulmonary hypertension. *Br Heart J* 1985,53·1–4
27 Fuster V, Steele PM, Edwards WD, Gersh BJ, McGoon MD, Frye RL Primary pulmonary hypertension natural history and the importance of thrombosis *Circulation* 1984,70.580–7
28 Dresdale DT, Michtom RJ, Schultz M. Recent studies in primary pulmon-

ary hypertension including pharmacodynamic observation on pulmonary vascular resistance. *Bull N Y Acad Med* 1954;30.195–207.
29 Widimský J, Kasalický J, Dejdar R, Vysloužil Z, Lukeš M. Effect of reserpine on the lesser circulation in chronic pulmonary diseases. *Br Heart J* 1962;24:274–8.
30 Landmark K, Refsum AM, Simonsen S, Storstein O. Verapamil and pulmonary hypertension *Acta Med Scand* 1978;204 299–302.
31 Camerini F, Alberti E, Klugmann N, Salvi A Primary pulmonary hypertension: effects of nifedipine. *Br Heart J* 1980;44:352–6.
32 Rubin LJ, Peter RH. Oral hydralazine therapy for primary pulmonary hypertension. *N Engl J Med* 1980;302:69–73.
33 Watkins WD, Peterson MB, Crone RK, *et al*. Prostacyclin and prostaglandin E_1 for severe idiopathic pulmonary artery hypertension. *Lancet* 1980;1:1083
34 Rubin LJ, Groves BM, Reeves JT, Frosolono M, Handel F, Cato AE. Prostacyclin-induced pulmonary vasodilatation in primary pulmonary hypertension. *Circulation* 1982,66:334–8.
35 Kambara H, Fujimoto K, Wakabayashi A, Kawai C. Primary pulmonary hypertension beneficial therapy with diltiazem *Am Heart J* 1981;101. 230–1.
36 Packer M, Greenberg B, Massie B, Dash H. Deleterious effects of hydralazine in patients with primary hypertension. *N Engl J Med* 1982;306·1326–31.
37 Rich S, Ganz R, Levy PS Comparative effects of hydralazine, nifedipine and amrinone in primary pulmonary hypertension. *Am J Cardiol* 1983;52:1104–9.
38 Douglas JS. Hemodynamic effects of nifedipine in primary pulmonary hypertension. *J Am Coll Cardiol* 1983;2 174–9
39 McGoon MD, Vliestra MB. Vasodilator therapy for primary pulmonary hypertension. *Mayo Clin Proc* 1984,59:672–7.
40 Rich S, Brundage B, Levy PS. The effect of vasodilator therapy on the clinical outcome of patients with primary pulmonary hypertension. *Circulation* 1985;71:1191–6
41 Packer M. Vasodilator therapy for primary pulmonary hypertension Limitations and hazards. *Ann Intern Med* 1985;103:258–70.
42 Stumpe KO, Schmengler K, Bette L, *et al*. Persistent hemodynamic and clinical improvement after captopril in patients with pulmonary hypertension. *Herz* 1986,11:217–25.
43 Reeves JT, Groves BM, Turkevich D. The case for treatment of selected patients with primary pulmonary hypertension. *Am Rev Respir Dis* 1986;134:342–6.
44 Roskovec A, Montanes P, Oakley CM Factors that influence the outcome of primary pulmonary hypertension *Br Heart J* 1986;55 449–58.
45 Jones DK, Higenbottam TW, Wallwork J. Treatment of primary pulmonary hypertension with intravenous epoprostenol (prostacyclin). *Br Heart J* 1987;57:270–8.
46 Rich S, Brundage B. High-dose calcium channel-blocking therapy for primary pulmonary hypertension: evidence for long-term reduction in pulmonary arterial pressure and regression of right ventricular hypertrophy. *Circulation* 1987;76.135–41
47 Roskovec A, Stradling JR, Shepherd G, MacDermot J, Oakley CM, Dollery CT. Prediction of favourable responses to long term vasodilator treatment of pulmonary hypertension by short term administration of epoprostenol (prostacyclin) or nifedipine *Br Heart J* 1988;59 696–705
48 Dantzker DR, D'Alonzo GE, Gianotti L, Fuentes F, Nickeson D, Emerson M Vasodilators and primary pulmonary hypertension. Variability of long-term response. *Chest* 1989;95.1185–9.
49 Palevsky HI, Schloo BL, Pietra GG, *et al*. Primary pulmonary hypertension. Vascular structure, morphometry, and responsiveness to vasodilator agents *Circulation* 1989;80 1207–21.
50 Bourdillon PDV, Oakley CM. Regression of primary pulmonary hypertension. *Br Heart J* 1976;38 264–70.
51 Fujii A, Rabinovitch M, Matthews EC. A case of spontaneous resolution of idiopathic pulmonary hypertension. *Br Heart J* 1981,46·574–7
52 Packer M. Is it ethical to administer vasodilator drugs to patients with primary pulmonary hypertension? *Chest* 1989,95.1173–5
53 Kanemoto N, Sasamoto H Pulmonary hemodynamics in primary pulmonary hypertension. *Jpn Heart J* 1979,20.395–405.
54 Rich S, Levy PS. Characteristics of surviving and nonsurviving patients with primary pulmonary hypertension. *Am J Med* 1984;76·573–8.
55 Glanville AR, Burke CM, Theodore J, Robin ED. Primary pulmonary hypertension. Length of survival of patients referred for heart-lung transplantation. *Chest* 1987,91.675–81
56 Eysmann SB, Palevsky HI, Reichek N, Hackney K, Douglas P Two-dimensional and doppler echocardiography and cardiac catheterization correlates of survival in primary pulmonary hypertension *Circulation* 1989,79.353–60
57 McCarthy PM, Starnes VA, Theodore J, Stinson EB, Oyer PE, Shumway NE. Improved survival after heart-lung transplantation. *J Thorac Cardiovasc Surg* 1990,99:54–9.
58 Newman JH, Ross JC. Primary pulmonary hypertension: a look at the future *J Am Coll Cardiol* 1989;14·551–5.
59 Ruoslahti E, Pierschbacher MD. New perspectives in cell adhesion RGD and integrins. *Science* 1987,238:491–7.
60 Chang SW, Voelkel NF. Charge-related microvascular injury. *Am Rev Respir Dis* 1989;139 534–45
61 Hales CA, Kradin RL, Brandstetter RD, Zhu Y. Impairment of hypoxic pulmonary artery remodelling by heparin in mice. *Am Rev Respir Dis* 1983;128·747–51

Br Heart J 1991;66:122-9

ORIGINAL ARTICLES

Quantitative angiography after directional coronary atherectomy

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Abstract

***Objective*—To assess by quantitative analysis the immediate angiographic results of directional coronary atherectomy. To compare the effects of successful atherectomy with those of successful balloon dilatation in a series of patients with matched lesions.**

***Design*—Case series.**

***Setting*—Tertiary referral centre.**

***Patients*—62 patients in whom directional coronary atherectomy was attempted between 7 September 1989 and 31 December 1990.**

***Interventions*—Directional coronary atherectomy.**

***Main outcome measures*—Increase in minimal luminal diameter of coronary artery segment.**

***Results*—Angiographic success on the basis of intention to treat was obtained in 54 patients (87%). In four patients the lesion could not be crossed by the atherectomy device; all four had an uneventful conventional balloon angioplasty. Four of the 58 patients who underwent atherectomy were subsequently referred for coronary bypass surgery because of failure or complications; three of them sustained a transmural infarction. In the successful cases, coronary atherectomy resulted in an increase in the minimal luminal diameter from 1·1 mm to 2·5 mm with a concomitant decrease of the diameter stenosis from 62% to 22%. In the subset of 37 patients in which the changes induced were compared with conventional balloon angioplasty atherectomy increased the minimal luminal diameter more than balloon angioplasty (1·6 *v* 0·8 mm; p < 0·0001). Conventional histology showed media or adventitia in 26% of the atherectomy specimens. In hospital complications occurred in six patients who had undergone a successful procedure: two transmural infarctions, two subendocardial infarctions, one transient ischaemia attack, and one death due to delayed rupture of the atherectomised vessel. All patients were clinically evaluated at one and six months. One patient had persisting angina (New York Heart Association class II), one patient sustained a myocardial infarction, one patient underwent a percutaneous transluminal coronary angioplasty for early restenosis, and one patient underwent coronary bypass surgery because of a coronary aneurysm formation. At six months 80% (36/47) of the patients were symptom free.**

***Conclusions*—Coronary atherectomy achieved a better immediate angiographic result than balloon angioplasty; however, in view of the complication rate in this preliminary series, which may be related to a learning curve, a randomised study is needed to show whether this procedure is as safe as a conventional balloon angioplasty.**

Percutaneous transluminal coronary angioplasty was reported in 1978 by Gruentzig[1] as a non-operative technique for the treatment of single, discrete, and proximal coronary artery stenosis in patients with symptomatic ischaemic heart disease. Over the past decade improved technology and operator experience have led to a greater use of conventional coronary angioplasty with an excellent immediate success rate.[2 3] As indications for coronary angioplasty expanded and more difficult lesions were attempted, the likelihood of acute complications increased. The most dangerous complication is acute occlusion which is encountered in 2–10% and frequently requires emergency surgical revascularisation.[4 5] Although acute occlusion is occasionally caused by thrombosis, it is usually caused by an intimal dissection.[6 7] In particular lesions with a complex shape have a greater tendency to occlude abruptly.[4] The use of new techniques might reduce acute complications after conventional balloon dilatation.[8-11] Although balloon angioplasty can efficiently dilate a stenosis, recoil is one of the immediate mechanisms that results in the loss of 50% of the balloon angioplasty result.[12] Several newly developed techniques have been designed to debulk coronary tissue thereby reducing the potential effect of elastic recoil.

Atherectomy is one such technique that might lead to fewer acute complications and less recoil because the plaque is removed rather than merely disrupted by the balloon inflation. There are published reports on the safety and short term results of atherectomy.[13-16]

We have assessed the immediate clinical and angiographic results of coronary atherectomy using quantitative coronary analysis as an objective method.

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Table 1 Clinical and angiographic characteristics in 58 patients who had atherectomy

Characteristic	*No*
Sex:	
Male	49
Female	9
Age (yr) mean (SD)	58 (10)
Infarction:	
Old	14
Recent	9
NYHA:	
II	18
III	17
IV	23
Stenosis:	
Primary	39
Restenosis	19
Anatomy:*	
LAD	37
LCx	9
RCA	15
Graft	3

*Four patients underwent two procedures, and one patient had three procedures.
NYHA, New York Heart Association; LAD, left anterior descending; LCx, circumflex artery; RCA, right coronary artery.

Patients and methods

PATIENTS

From 7 September 1989 to 31 December 1990, 62 patients underwent attempted directional coronary atherectomy at the Thoraxcenter. Four patients underwent two atherectomy procedures and one patient had three procedures. In four patients atherectomy was attempted but the stenosis could not be crossed by the device and all were subsequently treated by balloon angioplasty. All procedures were performed in patients with angina refractory to anti-ischaemic treatment. The study group (table 1) consisted of 49 men and nine women (mean (SD) age 58 (10)). A previous myocardial infarction was documented in 23 patients and nine of these patients were treated because of postinfarction angina. Four patients had prior surgical bypass grafting and 19 patients underwent atherectomy as a second percutaneous revascularisation procedure after previous conventional angioplasty ($n = 12$), after previous stenting ($n = 5$), or after previous atherectomy ($n = 2$). Two patients had a cardiac transplantation and another patient had had a kidney transplant. At the same time of atherectomy 23 patients were in New York Heart Association functional class IV, 17 in class III, and 18 in class II. Coronary angiography showed one vessel disease in 47 patients, two vessel disease in seven, and three vessel disease in four. The obstruction was in the left anterior descending artery in 37 procedures, in the right coronary artery in 15, in the circumflex artery in nine, and in the venous bypass graft in three cases.

Fifty two patients were selected for an elective atherectomy procedure and in six patients atherectomy was performed as an adjunct and bail-out procedure to a conventional balloon dilatation to prevent emergency coronary bypass surgery for the following reasons: obstructive dissection ($n = 4$), primary total occlusion ($n = 1$), and reocclusion after balloon angioplasty ($n = 1$). Three atherectomy procedures were performed in patients who required prophylactic haemodynamic support by means of intra-aortic counterpulsation ($n = 1$) or by percutaneous cardiopulmonary support ($n = 2$).

PROCEDURE

After administration of local anaesthesia a 11 French sheath was inserted into the femoral artery. All patients were given 250 mg aspirin and 10 000 U heparin intravenously. Then a 7 French guiding catheter was placed in the ostium of the coronary artery for initial angiograms in multiple views. This was replaced by the special 11 French guiding catheter. Then the atherectomy device (fig 1) was advanced by the over the wire technique and positioned across the stenosis. After proper positioning the support balloon was inflated up to 0·5 atmospheres, the cutter was retracted into the housing, and balloon inflation pressure was increased to 2 to 3 atmospheres. The driving motor was activated and the rotating cutter was slowly advanced to cut and collect the protruding intimal lesion in the collecting chamber located at the tip of the catheter. After each pass (mean (SD) 6·1 (2·9)) the balloon was deflated and either removed or repositioned. Atherectomy was regarded as successful when the residual stenosis was less than 50% of the vessel diameter and plaque material was present in the collecting chamber. After atherectomy the arterial and venous sheaths were usually left in place for six hours. Patients were monitored for 24 hours; electrocardiograms were obtained twice a day and cardiac enzyme concentrations measured twice a day. Nifedipine was given every two hours for 24 hours after the procedure and aspirin was given for one year. All atherectomy procedures were performed after the patient had given informed consent.

QUANTITATIVE CORONARY ANGIOGRAPHY

Quantitative analysis of the coronary segments was performed with the computer based Coronary Angiography Analysis System (CAAS), described in detail elsewhere.[17,18] In essence, the boundaries of a selected coronary artery segment were detected automatically

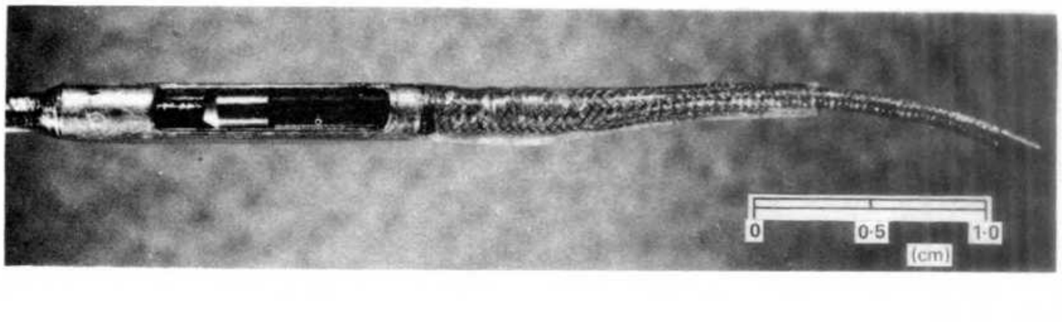

Figure 1 Simpson's directional AtheroCath.

from optically magnified and video digitised regions of interest (512 × 512 pixels) of a cineframe. The absolute diameter of the stenosis in mm was determined with the guiding catheter as a scaling device. Calibration of the catheter as an absolute value (mm) was achieved by comparing the mean diameter of the guiding catheter in pixels with the measured size in millimetres. Each catheter was measured individually. To correct the detected contour of the arterial and catheter segments for pincushion distortion, a correction vector was computed for each pixel based on a computer-processed cineframe with a centimetre grid placed against the input screen of the image intensifier. Because the functional significance of a stenosis is related to the expected normal cross sectional area of a vessel at the point of obstruction, we used a computer estimation of the original dimension of the artery at the site of the obstruction to define the interpolated reference area. The percentage diameter and area stenosis and the minimal luminal diameter (mm) and cross sectional area (mm^2) were then calculated. The length of the lesion (mm) was determined from the diameter function on the basis of a curvature analysis. In addition, this technique allowed the assessment of the eccentricity of the lesion for a given view. The symmetry index ranged from 0 (totally eccentric stenosis) to 1 (symmetric). The degree of coronary bend was assessed by the curvature value at the obstruction site. This variable was computed as the average value of all the individual curvature values along the centreline of the coronary segment, with the curvature defined as the first derivative of the tangent as it moves along the centreline, which for a circle is equal to the reciprocal of the radius.

ANGIOGRAPHIC MATCHING PROCESS

We compared the results of the first 37 successful consecutive patients of this series with the results of 37 individually matched angioplasty lesions in 37 other patients. To avoid patient selection bias we selected populations with comparable baseline stenosis characteristics. The coronary artery tree was subdivided into 15 segments according to the American Heart Association guidelines. The lesions were individually matched according to stenosis location and reference diameter. Matching was considered adequate if the mean difference of the reference diameter between the groups was zero.[19]

HISTOLOGY

Tissue samples were carefully removed from the collecting chamber of the atherectomy device. Part of the material was used for microscopical and morphological examination while the other part was processed for cell culture studies.[20] Specimens were fixed in 10% buffered formalin and embedded in paraffin. Tissue sections were cut and stained with haematoxylin-azofloxin. Light microscopical examination of each specimen was performed

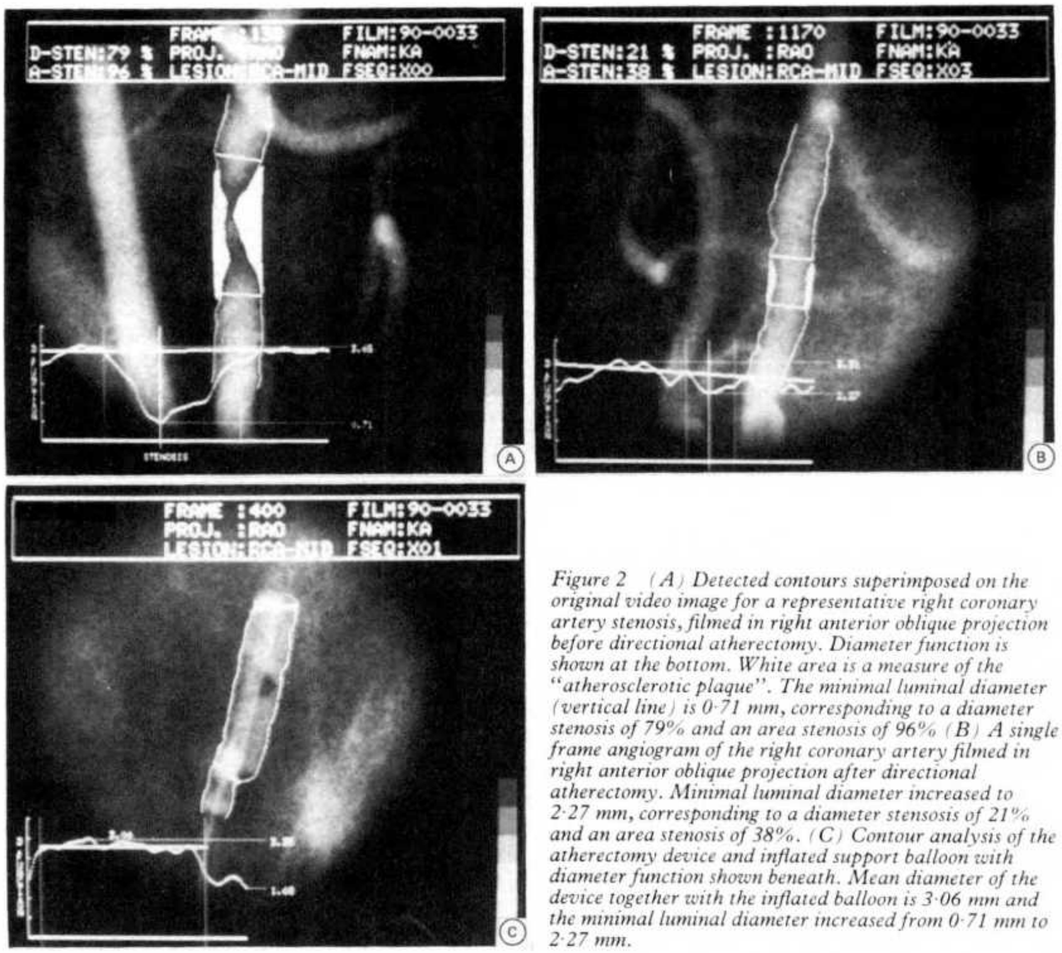

Figure 2 (A) Detected contours superimposed on the original video image for a representative right coronary artery stenosis, filmed in right anterior oblique projection before directional atherectomy. Diameter function is shown at the bottom. White area is a measure of the "atherosclerotic plaque". The minimal luminal diameter (vertical line) is 0·71 mm, corresponding to a diameter stenosis of 79% and an area stenosis of 96% (B) A single frame angiogram of the right coronary artery filmed in right anterior oblique projection after directional atherectomy. Minimal luminal diameter increased to 2·27 mm, corresponding to a diameter stensosis of 21% and an area stenosis of 38%. (C) Contour analysis of the atherectomy device and inflated support balloon with diameter function shown beneath. Mean diameter of the device together with the inflated balloon is 3·06 mm and the minimal luminal diameter increased from 0·71 mm to 2·27 mm.

to identify intima, media, and adventitia. Special attention was paid to the morphological structure of the removed tissue. Three types of lesions were encountered: atherosclerotic plaque, intimal fibrous proliferation, and thrombus. An atherosclerotic plaque was defined as dense fibrotic tissue while intimal hyperplasia was characterised by the proliferation of smooth muscle cells within a loose connective tissue matrix. Thrombus was defined as a laminar structure of fibrin, platelets, and erythrocytes. An organised thrombus was characterised by capillary vessel ingrowth. Specimens obtained from stent patients were stained with monoclonal antibodies specific for desmin, vimentin, and α smooth muscle actin.

Results

PROCEDURAL AND ANGIOGRAPHIC RESULTS

Sixty two patients underwent 68 attempts at atherectomy. Atherectomy was not possible in four patients for technical reasons. On two occasions the guiding catheter would not fit properly into the coronary ostium and on two occasions the atherectomy device could not pass the stenosis. These patients subsequently underwent conventional coronary angioplasty. Thus 58 patients underwent atherectomy in 64 lesions.

Sufficient atheroma was removed to reduce the angiographic stenosis to $<50\%$ of the reference diameter in 54 (93%) of 58 patients or in 60 (94%) of 64 stenoses. Additional balloon dilatation was never required and all patients left the catheterisation suite with a residual stenosis of $<50\%$ of the reference diameter. Figure 2 shows a quantitative angiographic analysis of a successful atherectomy procedure in a right coronary artery. For the lesions successfully treated the mean diameter stenosis decreased from 62 (11)% to 22 (12)%. Three patients underwent a conventional balloon angioplasty of other coronary stenoses after the successful atherectomy procedure.

Atherectomy was regarded as unsuccessful in four patients (7%) or in four stenoses (6%). All had a residual stenosis of $>50\%$ of the reference diameter. Three of four patients underwent emergency coronary artery bypass surgery and one had an semi-elective operation 24 hours after atherectomy. This last patient initially underwent a conventional balloon angioplasty of a totally occluded left anterior descending artery which was unsuccessful despite long inflation times and the use of an oversized balloon. To avoid bypass surgery, an initially successful bail-out atherectomy of the totally occluded artery was performed. After 10 minutes, however, the artery became reoccluded with contrast staining in the roof of the artery, though no signs of myocardial ischaemia were present. On the next day the patient underwent a semi-elective coronary bypass grafting operation. One of the three patients who underwent an emergency bypass operation had had a successful atherectomy procedure of the circumflex artery. An attempt to cross the second stenotic lesion in the left descending coronary artery with the device through a considerable bend, however, led to a dissection which resulted in ischaemic electrocardiographic changes and chest pain. Intra-aortic balloon pumping was initiated and the patient was subsequently sent for emergency bypass surgery. In the second patient introduction of the guiding catheter into the right coronary artery was complicated by an obstructive dissection with subsequent chest pain. The patient was referred for emergency surgery. A third patient underwent an emergency bypass operation after atherectomy because immediately after the atherectomy procedure this patient developed chest pain and ischaemic electrocardiographic changes owing to a total occlusion of the treated left

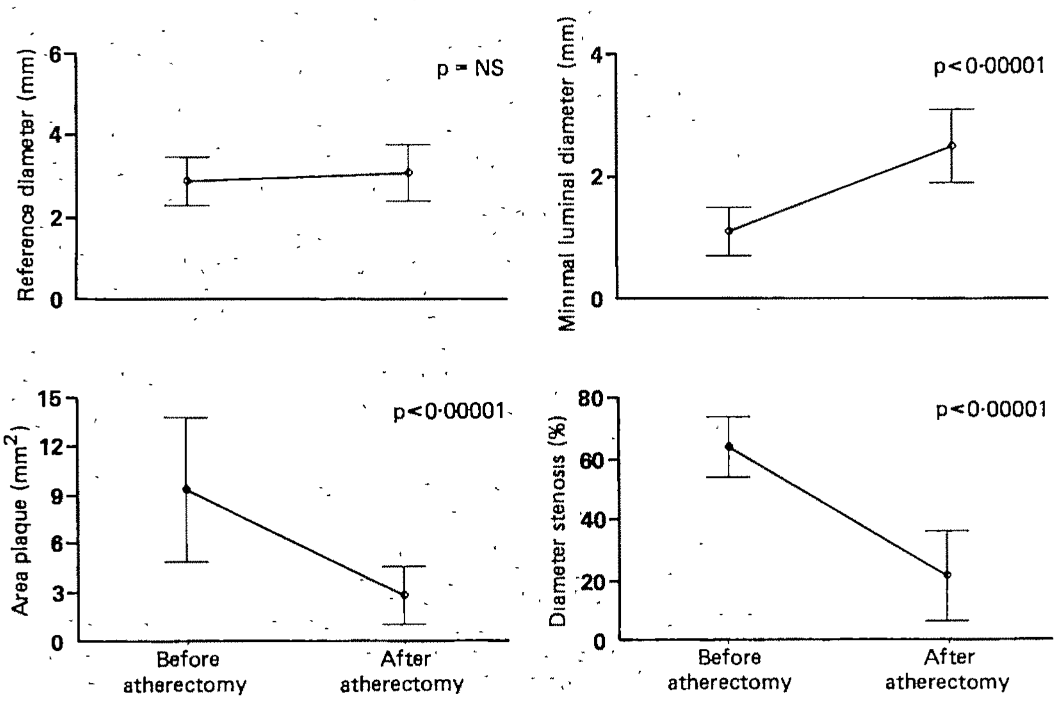

Figure 3 Changes in reference diameter, obstruction diameter, area plaque, and diameter stenosis before and after coronary atherectomy. Reference diameter did not increase significantly, obstruction diameter increased from 1·1 (0·4) mm to 2·5 (0·5) mm, area plaque decreased from 9·1 (6·3) mm² to 2·6 (1·8) mm², and diameter stenosis decreased from 62 (11)% to 22 (15)%.

anterior descending coronary artery. Before operation a stent was successfully implanted in a bail-out operation.

QUANTITATIVE CORONARY ANGIOGRAPHY

The mean (SD) length of the diseased segment was 6·4 (2·5) mm. The symmetry score showed that 59 of the 64 lesions were eccentric (symmetry index $< 1{\cdot}0$). The mean curvature value for all analysed segments was 14·5 (7·1). On average the minimal luminal diameter before atherectomy was 1·1 (0·4) mm. Post-atherectomy it increased to 2·5 (0·5 mm) ($p < 0{\cdot}00001$) (fig 3). The diameter stenosis decreased from 62 (11)% to 22 (15)% ($p < 0{\cdot}00001$), likewise the area stenosis decreased from 84 (9)% to 37 (18)% ($p < 0{\cdot}00001$). The reference diameter remained unchanged. The atherectomy device itself was also quantitatively analysed on the cinefilms. The mean diameter of the housing at its widest diameter was 2·1 mm. Inflation of the support balloon resulted in a diameter increase to 3·4 mm (2·1–4·3 mm).

IN-HOSPITAL COMPLICATIONS

Table 2 summarises the complications during the hospital stay. Six of the 54 patients who underwent a successful atherectomy procedure developed in-hospital complications. Two patients sustained a transmural and two a subendocardial myocardial infarction owing to embolisation of plaque material ($n = 2$), side branch occlusion ($n = 1$), or distal occlusion of the treated artery ($n = 1$). None of these patients needed an additional intervention and all of them left hospital without angina. One patient sustained a transient ischaemic attack, but completely recovered within three hours. One patient died of a delayed rupture of the atherectomised vessel three days after a "bail-out" atherectomy for an obstructive dissection after balloon dilatation.[20]

In one patient we faced a serious technical problem. This patient underwent an atherectomy of the left anterior descending coronary artery. During the last cutting pass the collecting chamber broke off the housing, migrated to the periphery of the coronary artery, and closed the distal part of the vessel. This caused chest pain and ischaemic electrocardiographic changes. Fortunately we were able to retrieve the collecting chamber by passing a conventional balloon on the wire catheter through the nose and inflating the balloon in the collecting chamber so that the distal part could be pulled back. Thereafter both the pain and electrocardiographic changes disappeared and the patient's recovery was uneventful without signs of a myocardial infarction.

The three patients who were referred for emergency coronary bypass surgery after an unsuccessful atherectomy procedure sustained a perioperative myocardial infarction. All patients had an uncomplicated postoperative clinical course and were discharged without anginal symptoms. The patient who underwent a semi-elective bypass operation had no complications at follow up examination.

Table 2 Complications of atherectomy

Complication	*Details*	
Non-Q infarct	2	After a successful procedure
Q wave infarct	5	Three perioperative infarctions
TIA	1	Without consequences
Death	1	Three days after a successful procedure
CABG	4	Three emergency, one semi-elective
PTCA	0	

CABG, coronary artery bypass grafting; PTCA, percutaneous transluminal coronary angioplasty; TIA, transient ischaemic attack.

ATHERECTOMY VERSUS ANGIOPLASTY

Matching according to lesion distribution and reference diameter was regarded as adequate because the reference diameter was equal in both groups (3·0 (0·6) mm) and the mean difference between the groups was 0·0 (0·2) mm. No differences were found before the procedure between the atherectomy and angioplasty groups: minimal luminal diameter (1·1 (0·4) mm *v* 1·1 (0·3) mm), diameter stenosis (63 (10)% *v* 63 (9)%), area plaque (9·1 (6·0) mm^2 *v* 8·4 (4·6) mm^2), and symmetry value (0·5 (0·3) *v* 0·4 (0·3)). The curvature value in the atherectomy group was less than in the angioplasty group (15·9 (7·0) *v* 22·2 (13·1)). Directional atherectomy increased the minimal luminal diameter from 1·1 (0·4) mm to 2·7 (0·4) mm and angioplasty increased it from 1·1 (0·3) mm to 1·9 (0·4) mm. In addition, the diameter stenosis decreased from 63 (10)% to 18 (8)% after atherectomy and from 63 (9)% to 36 (11)% after balloon dilatation. Similarly, the plaque area was reduced from 9·1 (6·0) mm^2 to 2·4 (1·7) mm^2 after atherectomy and from 8·4 (4·6) mm^2 to 5·3 (4·2) mm^2 after angioplasty. So the gain in lumen diameter with atherectomy was greater than that with balloon angioplasty (1·6 *v* 0·8 mm; $p < 0{\cdot}0001$).

HISTOLOGY

The appearance of the removed specimens was highly variable, ranging from translucent strips of white tissue to yellow tissue with brown areas corresponding to thrombus. Tissue samples of 62 of the 64 lesions were examined

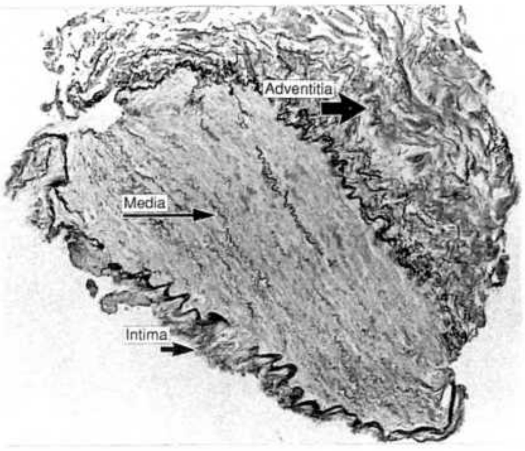

Figure 4 Haematoxylin-azofloxin stained histological cross-section through a specimen obtained by coronary atherectomy. This specimen contained all three vessel wall components. Internal elastic membrane between intima and media is clearly identified.

Table 3 Results of 6 month follow up

Complication	*No*
Angina	10
Infarction	1
PTCA/ath/stent	7
CABG	2
Death	0

ath, atherectomy; CABG, coronary artery bypass grafting; PTCA, percutaneous transluminal coronary angioplasty.

histologically. No histological specimen was available of the patient who died three days after the atherectomy procedure. The atherectomy specimens were scored for the presence of atheroslerotic plaque; intimal hyperplasia; thrombus; and media and adventitia. Atherosclerotic plaque was found in 35 specimens and intimal hyperplasia was present in 27. Intimal hyperplasia was found in 17 of 19 restenosis cases. Media was found in 16 patients; five of these specimens also contained adventitial tissue (fig 4). In five patients with restenosis after stenting, atherectomy was performed within the stent. Microscopical examination of the excised samples showed intimal hyperplasia with capillary ingrowth suggesting the presence of an organised thrombus. Immunohistochemical staining showed a positive reaction with antibodies for vimentin and alpha smooth muscle cell actin that was consistent with the presence of myofibroblasts.

CLINICAL FOLLOW UP

At one month 50 of the 54 patients who underwent a successful atherectomy were free of angina. One patient with incomplete revascularisation was in New York Heart Association functional class II, one patient suffered a myocardial infarction, one patient underwent a balloon angioplasty for early restenosis, and one patient had coronary bypass grafting eight days after a successful atherectomy procedure. This patient was operated upon because of a suspected pericarditis in the presence of a coronary aneurysm (shown on the coronary angiogram) and possible perforation. At surgery no pericardial fluid was found.

Forty six of the 54 patients who underwent a successful atherectomy procedure completed their six months clinical follow up (table 3). Thirty six patients (80%) had a persistent successful long term clinical course. Ten patients complained of recurrent angina: two were treated medically, four had a balloon angioplasty for restenosis, one underwent a second atherectomy procedure for restenosis, and one had an atherectomy for a new stenosis, one underwent stent implantation for restenosis, and one patient had a coronary bypass operation because of a restenosis with extensive three vessel disease.

Discussion

Although balloon angioplasty has excellent short term results with an initial success rate of over 90%,[2,3] a few complications can cause serious problems. Various pre-procedural angiographical risk factors have been identified for acute complications. Among these are lesion length, bend and branch point,[4] lesion eccentricity, calcification,[21,22] and myocardial jeopardy score.[23]

Acute coronary occlusion is the major cause of in-hospital morbidity and mortality. Such an acute coronary occlusion is usually secondary to a coronary dissection.[5,7] In experimental preparations dissections have been found most often in areas containing thick and multiple atherosclerotic plaques.[24] Therefore, it is not surprising that acute occlusion is related to lesion length, which seems to correlate with the amount of atherosclerotic material at the site of balloon inflation.

Because of these observations, conventional coronary angioplasty may not be the ideal non-operative treatment of large and eccentric plaque in proximal coronary artery disease. Recently, new techniques that remove the atherosclerotic plaque have been introduced for the treatment of obstructed coronary arteries.[8–11] Directional coronary atherectomy is one such new alternative to conventional angioplasty that is especially used for high risk lesions—that is, a long eccentric stenosis. In this series 92% had an eccentric score of $< 1·0$.

COMPARISON OF ATHERECTOMY AND BALLOON ANGIOPLASTY

With the advent of various new devices designed to treat coronary stenotic lesions it becomes difficult to define the proper indications. Directional atherectomy is currently used as an alternative to balloon angioplasty for the treatment of proximal large and eccentric plaque. Initial experience showed a high initial success rate with a reasonable complication rate.[13–16] But we do not know whether atherectomy is better than conventional balloon angioplasty for the treatment of eccentric coronary stenosis. So far there have been no prospective randomised trials to compare atherectomy with balloon angioplasty.

We used quantitative coronary artery analysis to assess the outcome of coronary atherectomy because it is the most objective method available. A computer based automatic edge detection angiographic analysis system such as this allows an accurate morphological description of the lesion that can be used to assess both the immediate and long term results of interventional techniques. When we closely matched stenoses treated by atherectomy with comparable stenoses treated by balloon angioplasty we found that atherectomy increased the minimal luminal diameter more than balloon angioplasty (1·6 *v* 0·8 mm; $p < 0·0001$). Although balloon angioplasty can efficiently dilate a lesion when the balloon is fully inflated, part of the luminal diameter increase will be lost due to the recoil phenomenon.[12] Remodelling by compression (the Dotter effect) accounts for some of the increase in luminal diameter after angioplasty. We do not know the extent of the contribution of the Dotter effect during directional atherectomy. This would require a randomised trial in which the three stages of the atherectomy procedure (crossing the stenosis by the device, subsequent inflation of the support balloon, and the cutting manoeuvre) were separately assessed by quantitative angiography. Such a study is precluded by ethical considerations.

Does the removal of atheromatous tissue explain the improvement in the luminal diameter? Rensing *et al* and others suggested that part of the luminal improvement is due to "facilitated angioplasty".[25,26] Our study helps to clarify this issue. The intracoronary quantitative assessment of the device size showed a mean diameter of 2·1 mm increasing to 3·4 mm after balloon inflation, while the minimal luminal obstruction diameter and reference diameter were 1·1 mm and 3·0 mm, respectively. The introduction of the atherectomy device itself has a "dottering" effect that is subsequently combined with an angioplasty effect when the support balloon is inflated.

Atherectomy was predominantly performed in long eccentric stenoses located in a proximal coronary artery containing a large atheromatous mass. Our primary angiographic success rate (87%), based on intention to treat analysis, is similar to the results reported so far.[13-16] The treatment of such a lesion is currently a major challenge in interventional cardiology because it is known that the risk of acute complication is high in these lesions. We need a randomised study to establish whether these lesions are more safely and successfully treated by atherectomy than by conventional balloon dilatation.

POTENTIAL RISKS

This new and vigorous technique produces a larger luminal diameter than any other intracoronary interventional technique.[25,27] Because the depth of the resection and precise spacial orientation of the device are not controlled, it is possible to remove both medial and adventitial tissue. In one study adventitia was identified in 30% of the resected specimens.[28] The 26% incidence of media in our specimens supports these findings.

In one of our patients coronary perforation occurred three days after a bail-out atherectomy. Conventional angioplasty had led to an obstructive dissection which was removed by atherectomy; three days later the patient died of cardiac tamponade. In one patient formation of a coronary aneurysm occurred after the use of a relatively oversized 7 F atherectomy device. Embolisation of atheromatous material from the plaque to the periphery of the treated vessel occurred in two patients resulting in a non-Q wave infarction. Side branch occlusion was noted once. With the use of an 11 French sheath, major groin complications may occur; however, none of our patients developed a haematoma requiring blood transfusion or vascular surgical repair. These cases underline the risks associated with the aggressiveness of atherectomy. In future the device will undoubtedly be modified to produce smaller, more flexible, and less traumatic systems.

ATHERECTOMY AS A BIOPSY TECHNIQUE

Recently Johnson *et al* reported their histological observations on excised peripheral arterial tissue from atherectomy procedures.[29] They found that 75% of restenosis showed intimal fibrous proliferation compared with 9% in primary atherectomy lesions which consisted predominantly of typical atherosclerotic plaque.[29] Our results are consistent with theirs: 89% of restenoses showed intimal hyperplasia compared with 24% of primary stenoses.

In our study atherectomy was performed within a stent on five occasions. The tissue excised resembled that of other restenosis specimens. Microscopy showed intimal hyperplasia and capillary ingrowth. Immunohistochemical staining showed that most of these cells were smooth muscle cells. We and others are currently investigating the behaviour of smooth muscle cells in culture from atherectomy material.[20,30] Thus atherectomy can be used to obtain material to throw light on the development of restenosis or to monitor pharmacological treatments.

Directional coronary atherectomy is an effective non-operative treatment of coronary artery lesions. It is particularly effective in removing atheromatous tissue specimens from eccentric lesions which are not particularly amenable to conventional balloon angioplasty. Quantitative analysis of the immediate results after coronary atherectomy shows a greater gain in minimal luminal diameter than with balloon angioplasty. Using quantitative analysis we found evidence that a facilitated angioplasty effect partly accounts for the luminal improvement. Because the depth and site of the resection is not controlled, atherectomy can lead to serious complications. Atherectomy is a method of obtaining human (re)stenosis tissue which can be used to study the causes of restenosis. Despite the encouraging short term results, however, we need further studies of the ultimate indications and long term follow up.

BHS is a research fellow of the Canadian Heart Foundation.

1 Gruentzig AR. Transluminal dilatation of coronary artery stenosis. *Lancet* 1978;**1**:263.

2 Dorros G, Cowley MJ, Simpson J, *et al*. Percutaneous transluminal coronary angioplasty: report of complications of the National Heart, Blood and Lung Institute PTCA registry. *Circulation* 1983;**67**:723–30.

3 Faxon DP, Kelsey SF, Ryan TJ, McCabe CH, Detre K. Determinants of successful percutaneous transluminal coronary angioplasty: report from the NHBLI registry. *Am J Cardiol* 1984;**108**:1019–23.

4 Ellis SG, Roubin GS, King SB, *et al*. Angiographic and clinical predictors of acute closure after native vessel coronary angioplasty. *Circulation* 1988;**77**:372–9.

5 de Feyter PJ, van den Brand M, Laarman GJ, van Domburg R, Serruys PW, Suryapranata H. Acute coronary occlusion during and after percutaneous transluminal coronary angioplasty: frequency, prediction, clinical course, management and follow up. *Circulation* 1991;**83**:927–36.

6 Block P, Myler R, Stertzer S, Fallon J. Morphology after transluminal angioplasty in human beings. *N Engl J Med* 1981;**305**:382–4.

7 Suryapranata H, de Feyter PJ, Serruys PW. Coronary angioplasty in patients with unstable angina pectoris: is there a role for thrombolysis? *J Am Coll Cardiol* 1988; **12**:69A–77A.

8 Waller BF. "Crackers, breakers, stretchers, drillers, scrapers, burner, welters and melters"—the future treatment of atherosclerotic coronary artery disease? A clinical morphologic assessment. *J Am Coll Cardiol* 1989;**13**: 969–87.

9 Simpson JB, Selmon MR, Robertson GC, *et al*. Transluminal atherectomy for occlusive peripheral vascular disease. *Am J Cardiol* 1988;**61**:96G–101G.

10 Fourier JL, Bertrand NE, Auth DC, Lablanche JM, Gommeaux A, Brunetaud JM. Percutaneous coronary rotational angioplasty in humans: preliminary report. *J Am Coll Cardiol* 1989;**14**:1278–82.

11 Stack RS, Quigley PJ, Sketch MH Jr, *et al*. Treatment of

coronary artery disease with the transluminal extraction-endarterectomy catheter initial results of a multicenter study [abstract]. *Circulation* 1989;80(suppl II):II–583.

12 Rensing BJ, Hermans W, Beatt KJ, *et al.* Quantitative angiographic assessment of elastic recoil after percutaneous transluminal coronary angioplasty. *Am J Cardiol* 1990;66 1039–44.

13 Vlietstra RE, Abbotsmith CW, Douglas JS, *et al.* Complications with directional coronary atherectomy. Experience at eight centers [abstract]. *Circulation* 1989;80 (suppl II):II–582.

14 Safian RD, Gelbfish JS, Erny RE, Schnitt DA, Baim D. Coronary atherectomy· clinical, angiographic, and histologic findings and observations regarding potential mechanism. *Circulation* 1990;82 69–79.

15 Robertson C, Hinohara T, Selmon M, Johnson DA, Simpson J. Directional coronary atherectomy. In· Topol EJ, ed *Textbook of interventional cardiology*. Philadelphia Saunders, 1990:563–79.

16 Garrat KN, Holmes DR, Bell MR, *et al* Restenosis after directional coronary atherectomy· differences between primary atheromatous and restenosis lesions and influence of subintimal tissue resection *J Am Coll Cardiol* 1990; 16:1655–71.

17 Serruys PW, Reiber JHC, Wijns W, *et al.* Assessment of percutaneous transluminal coronary angioplasty by quantitative coronary angiography: diameter versus densitometric area measurements *Am J Cardiol* 1984;54 482–8.

18 Reiber JHC, Serruys PW, Kooyman CJ, *et al.* Assessment of short-, medium- and long-term variations in arterial dimensions from computer-assisted quantitation of coronary cineangiograms. *Circulation* 1985;71 280–8.

19 Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurements. *Lancet* 1986;1:307–10.

20 Strauss BH, Verkerk A, van Suylen RJ, *et al* Smooth muscle cell culture from human coronary lesions [abstract]. *Circulation* 1990,82(suppl III): 496.

21 Fisch C, deSanctis RW, Dodge HT, Reeves J, Weinberg SL. Guidelines for percutaneous transluminal coronary angioplasty, a report of the ACC/AHA task force on assessment of diagnostic or therapeutic cardiovascular procedures. *Circulation* 1988,78:486–502.

22 Bredlau CE, Roubin G, Leimgruber P, Douglas J, King S, Gruentzig A In-hospital morbidity and mortality in patients undergoing elective coronary angioplasty *Circulation* 1985,72:1044–52.

23 Ellis SG, Roubin GS, King SB, *et al.* In-hospital mortality after acute closure after coronary angioplasty· analysis of risk factors from 8207 procedures. *J Am Coll Cardiol* 1988, 11 211–6

24 Zollikofer C, Chain J, Salomonowitz E, *et al.* Percutaneous transluminal angioplasty of the aorta. *Radiology* 1984,151· 355–60.

25 Rensing BJWM, Serruys PW, Laarman GJ, *et al* Directional coronary atherectomy, first Dutch experience with a new percutaneous revascularisation technique [in Dutch]. *Ned Tijdschr Geneeskd* 1990,134 962–7

26 Erny RE, Gelbfish JS, Safian RD, Diver DJ, Baim DS Does tissue removal explain all atherectomy improvement? [abstract] *Circulation* 1989,80(suppl II):582

27 Serruys PW, Strauss BH, van Beusekom HM, van den Giessen WJ. Stenting of coronary arteries. Has a modern Pandora's Box been opened? *J Am Coll Cardiol* 1991; 17·143B–54B.

28 Garratt KN, Kaufmann UP, Edwards WD, Vlietstra RE, Holmes DR Jr Safety of percutanous coronary atherectomy with deep arterial resection. *Am J Cardiol* 1989,64· 538–40.

29 Johnson DE, Hinohara T, Selmon MR, Braden LJ, Simpson JB. Primary peripheral arterial stenosis and restenosis excised by transluminal atherectomy a histopathological study. *J Am Coll Cardiol* 1990;15:419–25.

30 Dartch PC, Bauriedel G, Sckinko I, *et al* Cell constitution and characteristics of human atherosclerotic plaques selectively removed by percutaneous atherectomy *Atherosclerosis* 1989;80 149–57

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Early experience with low speed rotational angioplasty

Mark H Anderson, David E Ward

Abstract

Objective—Preliminary assessment of the efficacy and safety of the low speed rotational angioplasty catheter system (ROTACS).

Design—Open prospective trial.

Setting—Department of cardiology in a teaching hospital.

Patients—Eleven patients (10 with chronic stable angina and one with acute coronary occlusion after conventional angioplasty) in whom a coronary angiogram showed occlusion or critical stenosis of the coronary artery (right in seven patients, circumflex in two, and left anterior descending in two). The nature or severity of the lesion ruled out conventional coronary angioplasty.

Interventions—An attempt was made to cross the lesion with a rotating guide wire with a blunt swelling at its tip. Where necessary progress was assessed by simultaneous injection of contrast into both main coronary arteries.

Main outcome measures—Progress of the ROTACS through the lesion that allowed a guide wire to pass into the distal vessel was regarded as a device specific success. When a guide wire crossed the lesion aided only by the support of the ROTACS without the use of rotation this was counted as a success that was not device specific. Failure to cross the lesion and any associated complications were noted.

Results—The ROTACS crossed only two of the 10 chronic lesions (20% device specific success rate); however, the support it provided enabled a guide wire to cross a further two lesions and allowed subsequent successful angioplasty in four of the 10 patients. One of these four patients presented after five months with recurrent angina requiring bypass grafting. The other three were symptom free at follow up seven months after the procedure. In the one patient with acute coronary occlusion the ROTACS was advanced over the guide wire to allow passage of an angioplasty balloon where this had previously proved impossible. An excellent final result was obtained and this patient remains symptom free. Three of the six patients in whom the ROTACS was unsuccessful had coronary artery dissection without sequelae. Three patients required subsequent elective coronary bypass grafting for control of symptoms while the other three remain well on medical treatment.

Conclusions—The ROTACS may extend the range of patients with coronary artery occlusion or critical stenosis who can be treated non-surgically. The low device specific success rate (20%) achieved in this study indicates that it should be compared with other simpler mechanical devices that may be just as effective.

Coronary angioplasty has revolutionised the treatment of coronary artery stenoses but, because of its low success rate when used to attempt vessel recanalisation, it has had relatively little impact on the treatment of chronic coronary artery occlusion.

Various devices have been developed in an effort to improve the results of transcoronary attempts at recanalisation. In this study we describe our initial experience with the low speed rotational angioplasty system (ROTACS).

Patients and methods

We studied 11 patients (one woman and 10 men, aged 49–72 (mean 57·4)). Ten had a history of chronic stable angina. These 10 patients were referred for coronary arteriography, which showed complete occlusion or a critical coronary stenosis of a single coronary artery with or without important disease in the other coronary arteries (table). The severity of the coronary lesion was such that we would not have attempted conventional angioplasty. All patients had exercise tests showing ischaemic changes ($\geq 1 \cdot 5$ mm ST segment depression) in leads consistent with the site of critical stenosis or occlusion. The duration of occlusion or critical stenosis, estimated from sudden appearance of angina or occurence of a myocardial infarction, ranged from four to 31 months (mean 13 months). Informed consent was obtained from all patients.

EQUIPMENT

The device evaluated in this study was the rotational transluminal angioplasty catheter system (ROTACS) manufactured by Dr Ing

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Data on patients treated with the ROTACS

No	*Age*	*Vessel attempted*	*Age of lesion*	*Length of lesion (cm)*	*TIMI grade*	*1, 2, or 3 vessel disease*	*NYHA grade angina/ SOB*	*ROTACS size (mm)*	*Outcome*	*Complications*	*Current state*
1	52	RCA	?	3·0	2	Single	3/1	1·2	Success	—	Well after single CABG
2	72	RCA	9/12	3·8	1	Single	1/2	1·2	Failure	False lumen + limited dissection	Stable on medical treatment
3	60	RCA	8/12	3·6	2	Double	2/1	1·2	Success	—	Back at work
4	60	RCA	18/12	2·1	0	Double	2/1	1·2	Failure	False lumen + limited dissection	Symptom free and at work
5	49	RCA	5/12	3·7	0	Triple	2/1	1·4	Failure	Extensive dissection	Well after triple CABG
6	54	Cx	9/12	0·5	0	Single	1/2	1·2	Failure	—	Remains stable on medical treatment
7	54	LAD	24/12	1·2	1	Single	3/3	1·2	Success	Staphylococcal septicaemia	Symptom free
8	55	Cx	12/12	0·6	2	Double	2/1	1·2	Success	—	Symptom free
9	50	RCA	4/12	3·0	1	Single	2/1	1·2	Failure	—	Awaiting CABG
10	67	RCA	31/12	1·0	1	Single	2/1	1·4	Failure	—	Stable on medical treatment
11	58	LAD	Acute (during PTCA)	0·8	0	Single	2/1	1·4	Success	—	Symptom free

TIMI grading system: grade 0, no anterograde flow beyond point of occlusion; grade 1, contrast passes beyond obstruction but "hangs up" and fails to opacify the entire distal coronary bed; grade 2, contrast passes beyond obstruction opacifying the distal coronary bed and rate of entry or clearance of contrast is retarded; CABG, coronary artery bypass grafting; Cx, circumflex coronary artery; LAD, left anterior descending coronary artery; PTCA, percutaneous transluminal coronary angioplasty; RCA, right coronary artery; SOB, shortness of breath.

P Osypka GmbH (distributed in the UK by S-PACE). It consists of a flexible drive shaft with an olive shaped swelling (1·2, 1·4, or 1·6 mm diameter) at its tip (fig 1). The drive shaft is hollow and can take an 0·014 inch guide wire. The drive shaft is contained in a flexible sheath which provides support. This whole assembly is inserted through an 8 or 9 French gauge angioplasty guiding system. The proximal end of the drive shaft exits though a haemostatic valve and connects to a sterilisable battery powered variable speed motor unit (fig 1) that can drive the shaft at up to 200 rpm under load conditions.

PROCEDURE

Patients underwent routine preparation for coronary angioplasty and surgical cover was available for all procedures. The first two procedures were performed via the brachial route but the production of a longer ROTACS catheter enabled subsequent procedures to be performed from the femoral artery. A check angiogram was performed to assess the length of the occlusion or stenosis. Where there was no anterograde filling of the distal segment the other main coronary artery was catheterised simultaneously from the left femoral artery. This enabled visualisation of both left and right coronary systems with the collateral supply opacifying the distal segment (fig 2). The table shows the TIMI perfusion score[1] of the vessels attempted.

After 10 000 IU of heparin had been given the guiding system was introduced into the culprit vessel. We attempted to cross the occlusion/stenosis with a guide wire (0·014 inch high torque intermediate or standard) alone but this was invariably unsuccessful (cost considerations precluded the use of an angioplasty balloon to support the guide wire). The ROTACS was then passed via the guiding system into the coronary artery. The olive shaped head was rotated as it was moved slowly forward out of the supporting catheter and into the lesion (fig 3). Its progress was assessed periodically by contrast injection

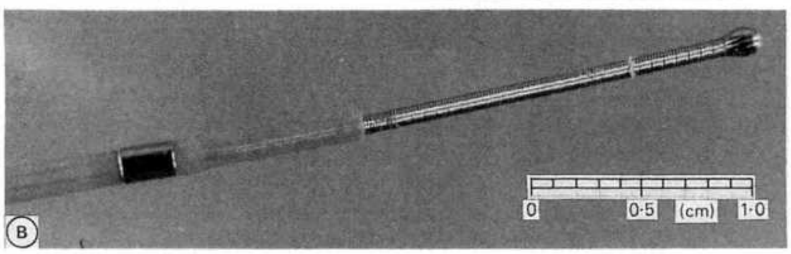

Figure 1 The ROTACS (A). A battery powered motor drive unit drives a flexible stainless steel drive shaft that emerges from its supporting catheter to terminate in (B) an olive-shaped tip.

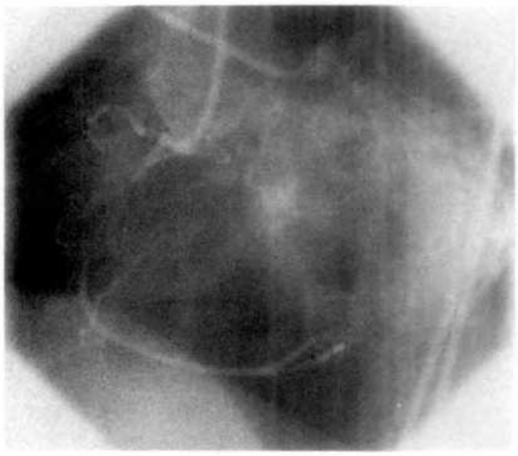

Figure 2 Angiogram of right coronary artery showing opacification of occluded distal segment by collateral flow from a second catheter in the left coronary artery.

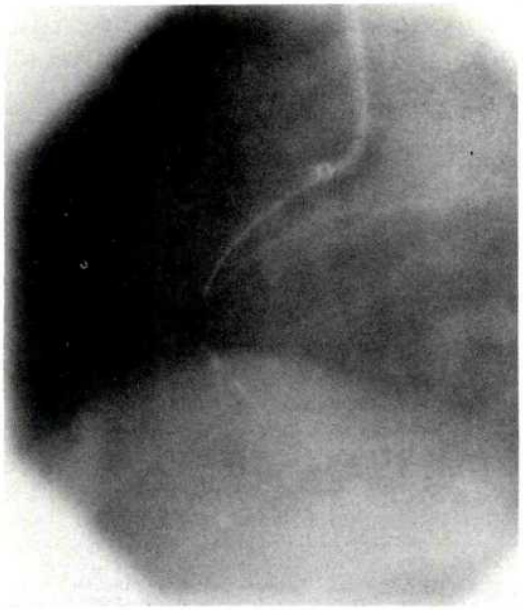

Figure 3 The ROTACS advancing from the guide catheter into a right coronary occlusion.

through the guiding system and, if necessary, retrograde opacification from the other coronary artery. When successful an 0·014 inch high torque floppy exchange wire was advanced out of the central lumen of the drive shaft and left in position across the lesion while the ROTACS was exchanged for a conventional balloon angioplasty catheter. The small size of the lumen created by the device meant that further angioplasty was invariably required. After angioplasty all patients were routinely treated with a calcium antagonist and aspirin.

Results

The table summarises the individual results. On only two occasions did the ROTACS drill successfully through a chronic coronary lesion (fig 4). On two other occasions it provided additional support for the guide wire and enabled it to cross the lesion; however, it is possible that these lesions could have been crossed by a conventional guide wire supported by an angioplasty balloon. In one patient who had had acute coronary occlusion during angioplasty the device was successfully used over a guide wire to create a passage for an angioplasty balloon. Previous attempts to pass an angioplasty balloon over the wire and through the occlusion had failed.

In the remaining six patients we were not able to cross the lesion with the ROTACS. In three of these patients the drill seemed to make good progress through the lesion but subsequent contrast injection showed that the device had failed to enter the distal lumen and dissection proximal and distal to the lesion (fig 5). No sequelae followed these dissections which all occurred in the right coronary artery and in lesions on a curve. In two other patients instability of the guiding system prevented any progress being made with the ROTACS, and in the final patient, who had a lesion in a tortuous circumflex vessel, no progress was made. Thus in only 20% of the patients with chronic coronary lesions was the rotary action of the ROTACS device of importance in crossing the lesion.

FOLLOW UP

The patients in whom the procedure was successful have now been followed for seven months. Four (80%) remain symptom free and two returned to work within two weeks of the

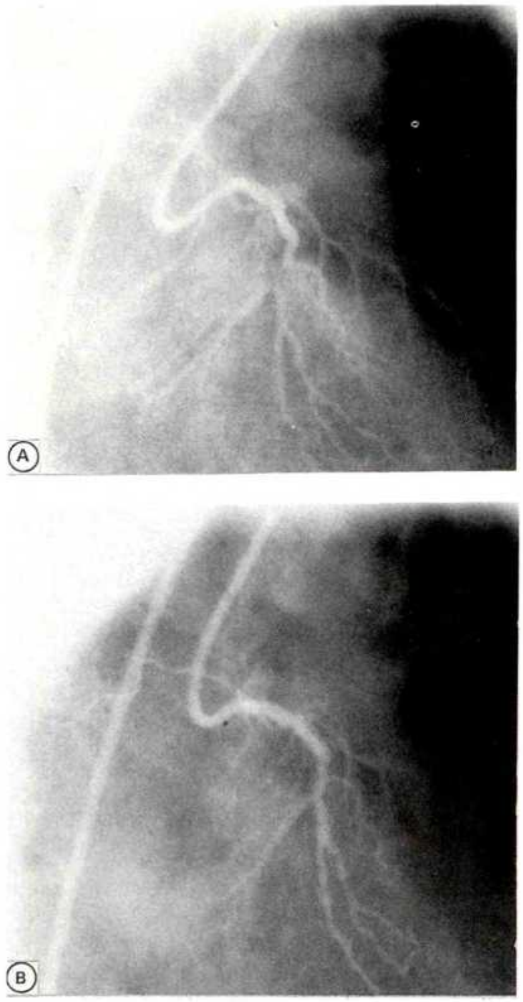

Figure 4 Successful rotational angioplasty of circumflex occlusion (A) before and (B) after use of the ROTACS and dilatation by conventional angioplasty balloon.

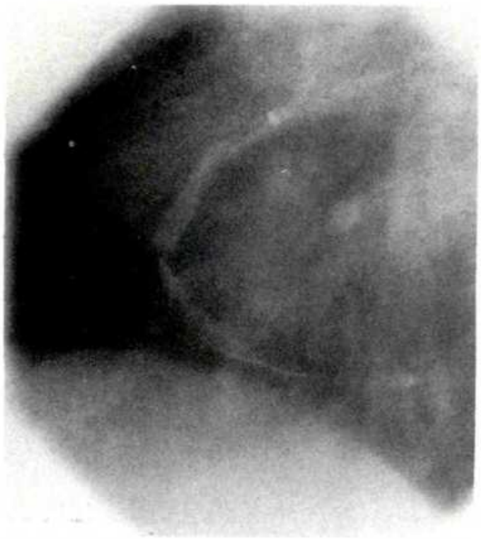

Figure 5 Proximal and distal dissection of the right coronary artery after a ROTACS procedure.

rotational angioplasty. The fifth patient was symptom free for five months and then presented with unstable angina caused by restenosis at the site of the original dilatation. She is now well after single vessel coronary artery bypass grafting.

Three (50%) of the patients in whom the procedure failed required non-emergency coronary artery bypass grafting for persistent symptoms. The other three remain well controlled on medical treatment alone.

Discussion

Conventional balloon angioplasty is an effective treatment for non-occlusive coronary disease and for acute coronary occlusions. The efficacy of angioplasty falls steadily as the age of occlusion increases.[2] Many other non-surgical approaches to reopening coronary occlusions are being assessed including the use of hollow guide wires,[3 4] the Magnum wire[5] (a 0·021 inch wire with an olive shaped swelling on its tip), ultrasound,[6] and laser and thermal energy.[7] Varying success rates have been reported for these treatments, though no formal comparison has been made of their relative efficacy. The ROTACS represents a development of the simple mechanical approach offered by the stiff guide wire but without the technical complexity and costs associated with laser and ultrasound. It uses a smooth, olive shaped swelling at the tip of a flexible drive shaft to displace the substance of the atheromatous plaque and enables passage of a guide wire and subsequent conventional angioplasty.

Kaltenbach and Vallbracht at the University of Frankfurt have the biggest current series of patients treated with the device. So far they have reported the use of the device in 60 patients selected because their coronary lesion could not be crossed by a guide wire.[8] Of these, 46 had right coronary artery occlusions, eight left anterior coronary artery occlusions, four circumflex artery occlusions, and two aorto-coronary bypass grafts with a mean duration of occlusion of 8·2 months. The success rate in the first 10 patients was 30% and this improved to 60% in the second 10 and subsequently remained at this level. They reported coronary artery dissection in three of their first 20 patients and in one subsequent patient who required emergency coronary artery bypass grafting.[9] They did not report any patients in whom a guide wire was able to cross the coronary lesion with solely the aid of the support provided by the ROTACS catheter. We report a lower device specific success rate (20%) and a higher incidence of complications, though fortunately none was serious. We also had problems with binding of the drive shaft on the internal guide wire, though this can be avoided by complete removal of the guide wire before rotation of the device.

The high incidence of arterial dissection noted in our patients is worrying. We found that in some patients the ROTACS successfully crossed an occlusion but then caused a dissection instead of entering the distal lumen. This was presumably because the ROTACS passed behind the intima and stripped it from the media. Once this occurs the device can travel in this plane of low resistance without re-entering the vessel lumen. In all our patients the lesion was probed with a guide wire before the ROTACS was used. Recently the manufacturer has advised against performing rotational angioplasty within one month of probing the lesion with a guide wire. This suggests that such probing may be a potential cause for the dissections noted.

Kaltenbach and Vallbracht reported follow up angiograms four months after angioplasty with a ROTACS in 17 patients.[10] Three (18%) showed a good result, eight (47%) had significant restenosis and had a successful repeat angioplasty, and six (35%) had re-occluded. We have not formally assessed restenosis with angiography but three of four patients remain symptom free while one required coronary artery bypass grafting for restenosis at the site of the occlusion.

From our small series of patients it is hard to draw conclusions about which features of the lesion can affect the success rate and incidence of subsequent restenosis. The effect of patient age, sex, duration of the occlusion, and the appearance of the occlusion and its position within the coronary tree remain unknown. From our experience the stiffness of the device and the need for torque transmission preclude its use in tortuous vessels. The use of the ROTACS for lesions on a curve may increase the incidence of vessel dissection.

We assessed the use of the ROTACS in patients with critical coronary stenoses and complete occlusions. The primary success rate was low and use of the device was associated with frequent vessel dissection. There was a high incidence of restenosis and re-occlusion. The efficacy and cost effectiveness of this device need to be compared with simpler mechanical devices such as the Magnum wire before its widespread use can be recommended.

1 The TIMI study group Special report, the Thrombolysis in Myocardial Infarction (TIMI) trial. *N Engl J Med* 1985, 312:932–6

2 Melchoir P, Meier B, Urban P, Finci L, Steffenino G Percutaneous transluminal coronary angioplasty for chronic total coronary arterial occlusion. *Am J Cardiol* 1987;59:535–8.

3 de Swart JB, van Gelder LM, van der Krieken AM, el Gamal MI A new technique for angioplasty of occluded coronary arteries and bypass grafts, not associated with acute myocardial infarction *Cathet Cardiovasc Diagn* 1987, 13 419–23

4 Smith LDR, Katritsis D, Webb-Peploe MM. Use of a hollow wire to facilitate angioplasty of occluded vessels. *Br Heart J* 1989;61 326–30.

5 Meier B, Carlier M, Finci L, *et al* Magnum wire for balloon recanalization of chronic total coronary occlusions. *Am J Cardiol* 1989,64 148–54.

6 Siegel RJ, Cumberland DC, Myler RK, Donmichael TA Percutaneous ultrasonic angioplasty initial clinical experience *Lancet* 1989,ii.772–4.

7 Litvack F, Grundfest WS, Segalowitz J, *et al*. Interventional cardiovascular therapy by laser and thermal angioplasty *Circulation* 1990,81 (suppl IV) 109–16

8 Kaltenbach M, Vallbracht C Low speed rotational angioplasty in chronic coronary artery obstructions [abstract] *Circulation* 1989,80(suppl II) 273

9 Kaltenbach M, Vallbracht C Reopening of chronic coronary artery occlusions by low speed rotational angioplasty *Journal of Interventional Cardiology* 1989;2,137–45.

10 Kaltenbach M, Vallbracht C, Kober G. Medium-term results after reopening chronic coronary artery obstructions by low speed rotational angioplasty [abstract] *Circulation* 1989,80 (suppl II) 257.

Br Heart J 1991;66:134–8

A pilot study of the efficacy and safety of bolus administration of alteplase in acute myocardial infarction

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Abstract

***Objective*—To examine the efficacy, safety, and the pharmacokinetic profile of a bolus dose administration regimen of alteplase in the treatment of acute myocardial infarction.**

***Design*—An open pilot study.**

***Setting*—District general hospital.**

***Patients*—33 suitable consecutive patients presenting within six hours of the onset of symptoms who satisfied the electrocardiographic criteria for acute myocardial infarction.**

***Interventions*—Two intravenous boluses of 35 mg alteplase, 30 minutes apart.**

***Main outcome measures*—Angiographic coronary patency at 90 minutes and 24 hours. Plasma alteplase concentration-time profile and pharmacokinetic analysis.**

***Results*—Coronary patency at 90 minutes: 26 of 30 arteries (87%, 95% confidence interval (CI) 74–99%). Coronary patency at 24 hours: 24 of 29 arteries (83%, CI 69–97%). Mean (SD) plasma tissue plasminogen activator (t-PA) concentration reached 4434·8 (2117·8) and 4233·3 (2217·5) ng/ml within 10 minutes of each bolus and fell to 425·8 (288·3) ng/ml between boluses. The estimated peak concentrations at two minutes after boluses were 12 389 (8580) ng/ml and 10 811 (6802) ng/ml. The derived pharmacokinetic variables were volume of distribution 3·11 (1·89) l, clearance 21·3 (9·3) l/h, half life 5·9 (1·7) minutes.**

***Conclusions*—This simple administration regimen achieved brief, high concentrations of plasma t-PA that were well tolerated. The regimen was associated with a high coronary patency rate at 90 minutes that was well maintained at 24 hours.**

Thrombolytic therapy is now accepted as a standard treatment for acute myocardial infarction because studies have shown that it improves left ventricular function and reduces mortality.[1–4] The benefit of thrombolysis is improved by early treatment[2,5] and the re-establishment of coronary patency. Therefore, the ideal thrombolytic agent should be easily and rapidly administered by the intravenous route and should effectively and rapidly restore coronary patency without adverse side effects. The ease of administration of the agent becomes increasingly important with the emphasis on immediate treatment on arrival in hospital and the possibility of starting treatment in the community.

Alteplase (recombinant tissue plasminogen activator) is successful in restoring coronary patency,[6–11] with higher patency rates than a conventional dose of intravenous streptokinase.[6,7] At present, the recommended dosage regimen for alteplase is a 10 mg bolus, with a tapering dose of 90 mg infused over three hours. This regimen was based on the apparent short half life of alteplase in the circulation,[12] but clearly this regimen is a cumbersome one to apply urgently.

We assessed the efficacy of two boluses of 35 mg alteplase administered intravenously 30 minutes apart in achieving angiographic coronary patency. We also studied the pharmacokinetics of this regimen.

Patients and methods

Thirty three consecutive patients (23 men and 10 women, age range 40–74, mean age 56·3 years) were admitted to Stobhill Hospital coronary care unit and recruited into the study. Patients were eligible for inclusion if they presented with chest pain of at least 30 minutes' duration, could be treated within six hours of the onset of symptoms, and had electrocardiographic evidence of acute myocardial infarction (ST elevation >1 mm in two limb leads or >2 mm in two precordial leads). Patients were excluded if they were over 75 years of age, had a previous infarct in the same anatomical distribution, or had any of the recognised contraindications to thrombolytic therapy[6] or coronary angiography. The study protocol was approved by the local research and ethics committee.

Table 1 shows the baseline characteristics of the patients recruited. After the patients had given their written informed consent and the protocol had been discussed with accompanying relatives, the patients were given 35 mg alteplase intravenously over 30 seconds. This dose was repeated 30 minutes later. All patients received 150 mg aspirin orally immediately on entry to the study and daily thereafter. All patients were given an intravenous infusion of glyceryl trinitrate

Table 1 Details of study population

Data	*Result*
Total	33
Sex:	
Male	23
Female	10
Mean age (yr)	56·3 (10·5)
Infarct related artery:	
LAD	12
RCA	15
LMCA	1
Cx	2
Angiography not performed	3
Mean (SD) time to therapy	208 (75) min
Mean (SD) time to first angiographic injection	49·4 (13·3) min
Mean weight	73·2 (12·8) kg
Dose of alteplase administered	70 mg
Mean dose of alteplase administered	0·984 (0·173) mg/kg

Cx, circumflex; LAD, left anterior descending; LMCA, left main coronary artery; RCA, right coronary artery.

starting at 0·25 mg/h unless there was a specific contraindication.

Coronary angiography was performed in the coronary care unit with an image intensifier (Siremobil 2N/2H) linked to a video tape recorder (JVC CR8200E). Details of this system have been described elsewhere.[13] The Seldinger percutaneous approach was used and a femoral sheath was left in situ. The coronary angiogram was started immediately after the second bolus of alteplase (30 minutes after the first bolus), and the infarct related coronary artery (as indicated by the admission electrocardiogram) was visualised as soon as possible after 30 minutes, then by selective injections at 60 and 90 minutes. The degree of perfusion was scored according to the Thrombolysis in Myocardial Infarction (TIMI) scale and reviewed by an independent experienced cardiologist: a score of 0–1 indicated non-patency and one of 2–3 indicated a patent artery.[6]

If the artery was occluded at 90 minutes, the study protocol allowed additional treatment to be given up to the total dose of 100 mg alteplase, as recommended by the product licence. The other coronary arteries were visualised in standard angiographic projections. The femoral sheath was left in situ and coronary angiography was repeated at 24 (8) hours after treatment to assess patency and reocclusion.

An intravenous heparin infusion was started in all patients 3–4 hours after onset of treatment, and the dose was titrated against the thrombin time to a therapeutic ratio of 2:3. No bolus of heparin was given at the start of alteplase treatment. In all patients heparin was stopped for a short period at the time of the second angiogram to allow removal of the femoral sheath. Venous blood samples were collected via an indwelling venous catheter from the first 24 patients before treatment, and then 10, 20, 30, 40, 50, 60 minutes and 2, 4, 8, 12, 24 hours after the first bolus of alteplase, into sodium citrate. The samples were centrifuged immediately at 0°C, separated, and frozen at −40°C. Subsequent analysis for antigen was performed by an enzyme linked immunosorbent assay (ELISA).

Results

ANGIOGRAPHIC PATENCY

The infarct related artery was first visualised at 49·4 (13·3) minutes after the first bolus of alteplase. The artery was visualised within 55 minutes in 26 of 30 (86%) patients. In three patients an acute angiogram was not obtained: in one because of haemodynamic instability, in one because of death before 90 minutes, and in one it was not possible to inject the right coronary artery.

In three patients, although the entry criteria were satisfied, the serial electrocardiographic changes of acute myocardial infarction did not occur and cardiac enzymes were normal. In one of these patients the right coronary artery could not be visualised and this patient is not included in the angiographic data. In all other patients angiographic data were obtained within 90 minutes of start of treatment and the results presented are the patency rates of all patients in whom coronary visualisation was achieved at each time point. At the first injection of the infarct-related artery (49·4 (13·3) mins) 23 of 30 (77%, 95% confidence interval (CI) 61 to 92%) arteries were patent. At 90 minutes this had increased to 26 of 30 (87%, 95% CI 74 to 99%) arteries (table 2).

Two patients were given a further intracoronary dose of 30 mg alteplase after the 90 minute angiogram. In one there was intermittent reperfusion of the index artery during the period of angiographic observation. In the other, after occlusion of the left main coronary artery, there was penetration only of the circumflex at 90 minutes. In both patients, the arteries were patent at the 24 hour angiogram.

One patient did not undergo the 24 hour angiogram because of haematoma formation after splitting of the femoral sheath. At 24 hours, 24 of 29 arteries (83%, 95% CI 69 to 97%) were patent. Seven patients improved their angiographic appearance by at least one grade, with three achieving reperfusion. However, five deteriorated at least one grade with three arteries becoming reoccluded (10%, 95% CI 0 to 22%).

ADVERSE EVENTS

The only adverse events documented in our study group were bleeding complications. In five patients significant haematomata developed at the site of arterial access for coronary angiography. Two patients suffered minor coffeeground haematemesis and one other bled from the gums. No patient required a blood transfusion or specific intervention.

One patient died during the study. This

Table 2 Angiographic details

	Number of patients			
	TIMI grade	*First injection 49·4 (13·3) min*	*90 min*	*24-h*
Non-patent	0	5	3	2
	1	2	1	3
Patent	2	15	18	10
	3	8	8	14
Reoccluded	—	—	0	0
Angiography not performed	—	3	3	4

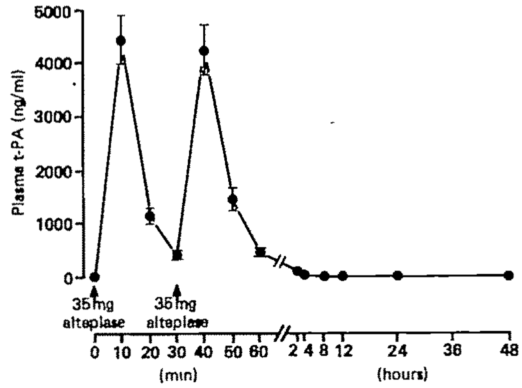

Figure Plasma t-PA concentrations (mean (SD)) after two intravenous boluses of 35 mg alteplase.

patient had severe triple vessel disease and a previous myocardial infarction. Shortly after admission and treatment cardiogenic shock developed and he died despite inotropic support.

PLASMA t-PA CONCENTRATIONS

The mean (SD) pretreatment plasma t-PA concentration (20·1 (4·3) ng/ml) was significantly higher than our laboratory normal (3·6 (1 3) ng/ml). It rose to 4434·8 (2117·8) ng/ml within ten minutes of the first bolus of alteplase, fell to 425·8 (288·3) ng/ml before the second bolus, and rose again to a peak of 4233·3 (2217·5) ng/ml within 10 minutes of the second bolus (figure). Mean concentrations then fell rapidly and at four hours were about twice the pretreatment values (40·6 (28·6) ng/ml). After this t-PA concentrations were low, variable, and at approximately physiological values. This introduced considerable random variation in the pharmacokinetic fitting; therefore the data fitted were the baseline-subtracted concentrations confined to the four hour period after the administration of alteplase. This approach was adopted by others.[12 14]

The individual declines in t-PA concentration were fitted to one, two, and three compartment pharmacokinetic models, but a satisfactory fit was obtained only with the one compartment model. The pharmacokinetic results derived from this model were volume of distribution 3·11 (1·89) l (coefficient of variation (CV) 35·6 (26·7)%), clearance 21·3 (9·3) l/h (CV 14·1 (11·7)%) and half life 5·9 (1·7) min. The coefficients of variation are means (SD) of the coefficients of variation of the individual fitted data and express the quality of fit of the model (table 3). Using this model we estimated the plasma t-PA concentrations two minutes after the beginning of the intravenous boluses of alteplase, as a measure of the peak concentrations achieved with this administration regimen. The peak concentration was 12 389 (8580) ng/ml two minutes after the first bolus and 10 811 (6802) ng/ml after the second bolus of alteplase.

Table 3 Pharmacokinetic variables

Variable	*Mean*	*SD*
Clearance (l/h)	21·4	9·3
Coefficient of variation of estimates of clearance (%)	14·1	11·7
Volume of distribution (l)	3·11	1·89
Coefficient of variation of estimates of volume (%)	35·6	26·7
Half life (min)	5·9	1·7

Discussion

Our results show that a regimen of alteplase administered intravenously as two boluses of 35 mg at an interval of 30 minutes is effective in restoring coronary artery patency in acute myocardial infarction. To allow comparison with other patency studies, our primary end point of efficacy was patency at 90 minutes after treatment, but in addition we have angiograms earlier in the course of treatment to assess the time to reperfusion. At the time of first injection, at a mean of 49 minutes after treatment, 77% of our patients had patent index coronary arteries; this improved to 87% within 90 minutes, showing that patency is achieved rapidly and effectively.

Direct comparison with other studies of recombinant tissue-type plasminogen activator (r-tPA) is difficult because of several confounding factors. Other studies used different administration regimens with widely varying doses of two different preparations of rt-PA, with different specific activities.[15 16] In addition, whereas some workers studied patency others studied reperfusion, with a difference owing to sub-total coronary occlusion at presentation and spontaneous reperfusion.[17]

Verstraete and coworkers showed patency rates of 61% at 75–90 minutes after treatment using 0·75 mg/kg of double chain rt-PA over 90 minutes.[11] The same group using a 40 mg infusion of double chain rt-PA over 90 minutes achieved a coronary patency rate of 66% at 90 minutes.[18] Topol and the TAMI group achieved a patency rate of 68% with 70 mg of rt-PA over 90 minutes and one of 79% with a high dose (1·5 mg/kg) of alteplase over four hours in conjunction with a high dose of heparin.[19–21] In TIMI I workers used 80 mg of double chain rt-PA over three hours and found a reperfusion rate of 56%.[6 7] Williams *et al* used the same dose of 80 mg over three hours and found a similar reperfusion rate of 68%.[8]

Published reports of studies of bolus doses of alteplase are limited. Verstraete *et al* using single boluses of alteplase found that doses of 60 mg and 50 mg were associated with reperfusion rates at 90 minutes of 32% and 45% respectively, although a maximum dose of 70 mg achieved reperfusion in 72%.[22] Khan *et al* evaluated four boluses of double-chain t-PA of 25 mg given over 60 minutes and showed recanalisation in 11 of 14 patients; they suggested that this regimen achieves coronary patency more rapidly.[23] In our study, 70 mg divided into two boluses also achieved a high patency rate, and would be expected to be associated with fewer bleeding complications.[24]

In a recent small study Smalling *et al*, used rapid intravenous infusion of a weight adjusted dose of alteplase, and a median dose of 145 mg. They reported a 90 minute patency rate of 84%, which was significantly higher than the control group who received a conventional three hour infusion of 100 mg.[25] These results suggest that rapid administration of the thrombolytic agent achieves higher patency, and that it is the peak concentration of agent achieved that is important—an inference supported by our data.

The reported higher patency rates were achieved with higher weight adjusted doses of rt-PA. In our study the total dose of 70 mg alteplase represents a mean dose of 0·98 mg/kg. This contrasts with 1·5 mg/kg administered by Topol *et al*[20] and the fixed doses of 150 mg used in the TIMI II study[24] or 100 mg used in the Australian National Heart Foundation Study.[26] The 100 mg dose is recommended by the manufacturers[27] and is now in regular use. Despite the lower dose we used, our patency rate of 87% at 90 minutes compares favourably with the published data.

Pharmacokinetic analysis of the plasma t-PA concentration-time profile after this bolus administration regimen of alteplase shows that very high, short lived concentrations of t-PA are achieved shortly after injection of the drug. The concentration of t-PA achieved at 10 minutes (4434·8 (2117·8) ng/ml is 34% higher than the peak concentration attained by Seifried *et al*, with 100 mg of single chain rt-PA delivered as a 10 mg bolus and 90 minute tapered infusion.[14] We found t-PA concentrations in excess of 2 300 ng/ml in all our patients and predicted concentrations two minutes after the boluses of alteplase in excess of 10 000 ng/ml. As would be expected, the period during which t-PA concentration was in excess of 1000 ng/ml is shorter with bolus administration than with prolonged infusion.

Despite the short duration of high plasma t-PA concentrations the reocclusion rate to 24 hours of three of 29 patients (10%) resembles previous experience.[18]

Our patients' pretreatment t-PA concentrations were raised, but 4–8 hours after alteplase concentrations fell to physiological values. After four hours in all patients, t-PA concentrations were low and variable, making fitting to pharmacokinetic models difficult. To eradicate this variable, we fitted the data for the first four hours only and used baseline-subtracted values. Despite taking frequent blood samples we were unable to define multiple phases of elimination, unlike others. Our data fitted our chosen model satisfactorily, as reflected in low standard deviations for each individually fitted variable. These individual standard deviations were expressed as coefficients of variation (CV) of their respective estimated variable and the CVs expressed as the mean. The mean CV of the estimate of mean clearance was 14% and that of the estimate of mean volume of distribution 36%, which indicates that the estimate of these mean variables was reliable. Previous studies have not reported details of the quality of fit of their models and therefore of the reliance that can be placed on their estimations.[12 14]

Our findings confirm the rapid clearance of t-PA from the circulation, with a half life of 5·9 (1·7) minutes and modest inter-patient variability. These closely correlate with previous reports in patients, although they are somewhat slower than findings in normal volunteers with a lower total dose—possibly reflecting diminished cardiac output and hepatic blood flow in our patients with myocardial infarction. Our estimate of volume of distribution of 3·1 (1·9) l is very similar to previous estimates in both patients and volunteers.

Some workers have found a dose related rise in bleeding complications, in particular intracranial bleeding.[24] In our study, using a relatively small dose of alteplase, we saw bleeding complications in eight (24%) of 33, with five of these being related to arterial access for coronary angiography; there were three episodes of minor gastrointestinal bleeding (9%). No patients required transfusion or specific intervention. These results are similar to previously published data,[6 9 10] but our small study numbers do not allow firm conclusions to be drawn.

Our findings show that alteplase administered as two intravenous boluses of 35 mg 30 minutes apart reliably produced very high concentrations of t-PA in the plasma, which was rapidly cleared from the circulation and allowed a high coronary patency rate in acute myocardial infarction. The total dose administered was less than that used in many studies reporting high patency, yet reocclusion rates were similar to those reported before. The greater simplicity of administration and higher efficacy of this regimen may allow alteplase treatment to be safely started before admission to hospital with the advantages that such earlier administration would give.

1 White HD, Rivers JT, Mastowski AH, *et al*. Effect of intravenous streptokinase as compared with that of tissue plasminogen activator on left ventricular function after first myocardial infarction *N Engl J Med* 1989,320·817–21.

2 Gruppo Italiano Per Lo Studio Della Streptochinasi Nell Infarto Miocardico (GISSI). Effectiveness of intravenous thrombolytic treatment in acute myocardial infarction *Lancet* 1986;i.397–401.

3 ISIS-2 Collaborative Group. Randomised trial of intravenous streptokinase, oral aspirin, both, or neither among 17187 cases of suspected acute myocardial infarctions. ISIS-2. *Lancet* 1988;ii:349–60.

4 Wilcox RG, Olssen CG, Skene AM, van der Lippe G, Jensen G, Hampton JR for the ASSET Study Group Trial of Tissue Plasminogen Activator for Mortality Reduction in Acute myocardial infarction. Anglo-Scandinavian Study of Early Thrombosis (ASSET). *Lancet* 1988;ii:525–30

5 Simoons ML, Serruys PW, van der Brand M, *et al*. Early thrombolysis in acute myocardial infarction limitation of infarct size and improved survival. *J Am Coll Cardiol* 1986,7:717–28.

6 TIMI Study group. The thrombolysis in myocardial infarction (TIMI) trial. Phase I findings. *N Engl J Med* 1985, 312:932–6.

7 Chesebro JH, Knatterud G, Roberts R, *et al*. Thrombolysis in myocardial infarction (TIMI) trial, Phase I: a comparison between tissue plasminogen activator and intravenous streptokinase. *Circulation* 1987;76:142–54.

8 Williams DO, Borer J, Braunwald E, *et al*. Intravenous recombinant tissue-type plasminogen activator in patients with, acute myocardial infarction: a report from the NHLBI thrombolysis in myocardial infarction trial. *Circulation* 1986;73:338–46.

9 Collen D, Topol EJ, Tiefenbrunn AJ, *et al*. Coronary thrombolysis with i.v. administered human tissue-type plasminogen activator a prospective, randomised, placebo-controlled trial. *Circulation* 1984;70·1012–7.

10 Verstraete M, Bernard R, Bory M, *et al*. Randomised trial of intravenous recombinant tissue-type plasminogen activator versus intravenous streptokinase in acute myocardial infarction. Report from the European Co-operative Study Group for Recombinant Tissue-type plasminogen activator *Lancet* 1985;i:842–7.

11 Verstraete M, Brower RW, Collen D, *et al* Double-blind randomised trial of intravenous tissue-type plasminogen activator versus placebo in acute myocardial infarction. *Lancet* 1985;ii.965–9.

12 Tanswell P, Seifried E, Su PGAF, Fenerer W, Rijken DC. Pharmacokinetics and systemic effects of tissue-type plasminogen activator in normal subjects. *Clin Pharmacol Ther* 1989,46 155–62.

13 Hillis WS, Jones CR, Been M, Campbell BC, Fulton WFM. Intracoronary thrombolytic therapy performed within a coronary care unit· one year's experience. *Scott Med J* 1986;31.25–9.

14 Seifried E, Tanswell P, Ellbruck D, Haerer W, Schmidt A. Pharmacokinetics and haemostatic status during consecutive infusions of recombinant tissue-type plasminogen activator in normal subjects. *Thromb Haemost* 1989,61:497–501.

15 Garabedian DH, Gold HK, Leinbach RC, *et al*. Comparative properties of two clinical preparations of recombinant human tissue-type plasminogen activator in patients with acute myocardial infarction. *J Am Coll Cardiol* 1987,9·599–607.

16 Muller HS, Rao AK, Forman SA. Thrombolysis in myocardial infarction (TIMI): comparative studies of coronary reperfusion and systemic fibrinogenolysis with two forms of recombinant tissue-type plasminogen activator *J Am Coll Cardiol* 1987;10 479–90.

17 de Wood MA, Spores J, Wotske R, *et al*. Prevalence of total coronary occlusion during the early hours of transmural myocardial infarction *N Engl J Med* 1980;303·897–902.

18 Verstraete M, Arnold AER, Brower RW, *et al*. Acute coronary thrombolysis with recombinant human tissue-type plasminogen activator, initial patency and influence of maintained infusion on reocclusion rate *Am J Cardiol* 1987;60·231–7

19 Topol EJ, Bates ER, Walton JA, *et al* Community hospital administration of intravenous tissue plasminogen activator in acute myocardial infarction: improved timing, thrombolytic efficacy and ventricular function. *J Am Coll Cardiol* 1987,10 1173–7.

20 Topol EJ, George BS, Kereiakes DJ, *et al*. A randomized controlled trial of intravenous tissue plasminogen activator and early intravenous heparin in acute myocardial infarction. *Circulation* 1989,79:281–6.

21 Topol EJ, Phillips HR, George BS, *et al* and the TAMI Study Group. Search for the optimal dose of intravenous tissue plasminogen activator for acute myocardial infarction. results from the TAMI Study [abstract]. *Circulation* 1987;76 (suppl iv)· 306

22 Verstraete MR, van der Werf F, Tranchesi B, Charmone DF, Pelaggi F Bolus alteplase. *Lancet* 1989;ii:989.

23 Khan MI, Hackett DR, Andreotti F, *et al*. Effectiveness of multiple bolus administration of tissue-type plasminogen activator in acute myocardial infarction. *Am J Cardiol* 1990,65.1051–6.

24 The TIMI Study group Comparison of invasive and conservative strategies after treatement with intravenous tissue plasminogen activator in acute myocardial infarction. Results of the Thrombolysis in Myocardial infarction (TIMI) Phase II trial *N Engl J Med* 1989;320. 618–27

25 Smalling RW, Schumacher R, Morris D, *et al*. Improved infarct-related arterial patency after high-dose, weight-adjusted, rapid infusion of tissue-type plasminogen activator in myocardial infarction: results of a multicentre randomised trial of two dosage regimens *J Am Coll Cardiol* 1990;15·915–21.

26 National Heart Foundation of Australia Coronary Thrombolysis Group. Coronary thrombolysis and myocardial salvage by tissue plasminogen activator given up to 4 hours after onset of myocardial infarction. *Lancet* 1988;i 203–8.

27 Actilyse Data Sheet (Boehringer Ingelheim Hospital Division) ABPI Data Sheet Compendium 1989–90. London· Datapharm Publications.

Zestril
lisinopril ICI
Prescribing Notes.

Consult data sheet before prescribing.
Use: All grades of essential hypertension and renovascular hypertension. Congestive heart failure (adjunctive therapy).
Presentation: Tablets containing 2.5mg, 5mg, 10mg or 20mg lisinopril ('Zestril').
Dosage and administration: Hypertension – initially 2.5mg daily, a 2.5mg dose seldom achieves a therapeutic response; adjust dose according to response. Maintenance usually 10-20mg once daily. Maximum is 40mg daily. Diuretic-treated patients – if possible stop diuretic 2-3 days before starting 'Zestril'. Resume diuretic later if desired.
Congestive heart failure: (adjunctive therapy) – initially 2.5mg daily in hospital under close medical supervision, increasing to 5-20mg once daily according to response.
Impaired renal function: May require a lower maintenance dose. 'Zestril' is dialysable.
Elderly patients: No change from standard recommendations.
Contraindications: Pregnancy – stop therapy if suspected. Hypersensitivity to 'Zestril'. Patients reacting with angioneurotic oedema to previous ACE inhibitor treatment.
Precautions: Assessment of renal function is recommended. Renal insufficiency; renovascular hypertension; surgery/anaesthesia: possibility of hypotension especially in ischaemic heart disease and cerebrovascular disease. Combination with antihypertensives may increase hypotensive effect. Sometimes increased blood urea and creatinine and/or cases of renal insufficiency if given with diuretics. Minimises thiazide-induced hypokalaemia and hyperuricaemia. Potassium supplements, potassium-sparing diuretics and potassium-containing salt substitutes not recommended. Indomethacin may reduce hypotensive effect. Possible reduced response in Afro-Caribbean patients. Use with caution in breastfeeding mothers. Do not use in aortic stenosis or outflow tract obstruction or cor pulmonale. Monitor lithium serum levels if lithium salts administered.
Side effects: Dizziness, headache, diarrhoea, fatigue, cough and nausea. Less frequently, rash and asthenia. Rarely, angioneurotic oedema and other hypersensitivity reactions, renal failure, symptomatic hypotension (especially if volume-depleted), severe hypotension (more likely if severe heart failure), palpitation, hyperkalaemia; increases in liver enzymes and serum bilirubin (usually reversible on discontinuation of 'Zestril') and impotence.
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PRECAUTIONS
Assess renal function prior to therapy with 'Innovace' and during therapy where appropriate.
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Combination with antihypertensives may increase hypotensive effect. In some patients with bilateral renal artery stenosis increased blood urea and creatinine has been seen, especially in patients treated with diuretics and/or those with renal insufficiency. Minimises thiazide-induced hypokalaemia and hyperuricaemia. Potassium supplements, potassium-sparing diuretics, and potassium-containing salt substitutes are not recommended.
Possible reduced response in Afro-Caribbean patients. Use with caution in breast-feeding mothers. Do not use in aortic stenosis, or outflow tract obstruction. Monitor serum levels of lithium, if lithium salts are given.

SIDE EFFECTS
Side effects include: dizziness, headache. Others include fatigue, asthenia, nausea, diarrhoea, muscle cramps, rash, cough.
Less commonly, angioneurotic oedema; other hypersensitivity reactions; renal failure; symptomatic hypotension (especially if volume-depleted); severe hypotension (more likely if severe heart failure); hyperkalaemia, hyponatraemia; increases in liver enzymes and serum bilirubin (usually reversible on discontinuation of 'Innovace'); paraesthesiae; impotence.

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References
1. Kjekshus, J., and Swedberg, K., *Amer. J. Cardiol.*, 1989, **63**, 26D.
2. Swedberg, K., and Kjekshus, J., *Drugs*, 1990, **39** (Suppl. 4), 49.
3. CONSENSUS Trial Study Group, *New Engl. J. Med.*, 1987, **316**, 1429.

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Br Heart J 1991;**66**:139–42

Immunoglobulin response to intravenous streptokinase in acute myocardial infarction

Mary Lynch, W A Littler, B L Pentecost, R A Stockley

Abstract

***Objective*—To devise assays to assess and follow the specific antibody response in patients treated with streptokinase for acute myocardial infarction.**

***Design*—Venous blood samples were collected before treatment with streptokinase started and subsequently at regular intervals over one year. Specific IgG and subclass IgG1 were assessed by an enzyme linked immunosorbent assay.**

***Setting*—Coronary care unit in a general hospital.**

***Patients*—48 patients with acute myocardial infarction: 22 patients had venous blood samples taken at presentation only; serial blood samples were taken from 20 patients who then received thrombolytic therapy with streptokinase and six patients who were unsuitable for thrombolytic therapy.**

***Results*—Titres of antibodies to streptokinase were low at presentation in 36 (75%) of the 48 patients. Serial measurements made in 20 patients showed the virtual disappearance of antibody within the first 24 hours. This was followed by a steady increase in the specific IgG1 titre, which peaked at day 14 before gradually declining. Values at one year remained significantly higher than baseline values. There was no evidence of an IgM response in the patients studied.**

***Conclusion*—Low titres of antibodies to streptokinase were widespread in the population. Antibody was consumed after treatment and the subsequent immunoglobulin rise suggested a secondary immune response; the recently described neutralising capacity to streptokinase is probably related to this antibody.**

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Thrombolysis is now a routine treatment for acute myocardial infarction. It improves morbidity by reducing infarct size and reduces overall mortality.[1 2] Streptokinase is the most widely used and least expensive thrombolytic agent; in the United Kingdom more experience has been gained with this agent than with any other. It is most often produced by β haemolytic streptococci group C but is also produced by groups A, D, and E. Because streptokinase is a foreign protein it is antigenic, unlike some other thrombolytic agents such as tissue plasminogen activator or urokinase. Studies of the dose of streptokinase required to achieve a thrombolytic state showed that antibodies to streptokinase were widespread in the community.[3 4] The presence of these antibodies raises the possibility of an adverse immune reaction after treatment with streptokinase.

There are few published reports on the allergic aspect of thrombolytic therapy with streptokinase and these are mainly anecdotal. The reported incidence of allergic reactions varies from 1·7% to 18%.[5] These reactions include acute anaphylaxis,[5] serum sickness,[6–8] and delayed hypersensitivity.[9] Nevertheless, the relation of the reactions to the immune response is poorly understood. Currently, it is recommended that streptokinase treatment should not be repeated between three days and six months after the initial dose.

The purpose of the present study was to devise assays to assess and follow the antibody response in patients given streptokinase for acute myocardial infarction so that the safety of streptokinase therapy can be determined more reliably.

Patients and methods

We studied 48 patients (38 men and 10 women, aged 42–80), with acute myocardial infarction. Myocardial infarction was diagnosed on the basis of chest pain and definite electrocardiographic changes (ST elevation > 2 mm or T wave inversion in both). Twenty two of the patients had a venous blood sample taken at presentation only. A further 20 patients who were suitable for thrombolytic therapy with streptokinase and six patients in whom streptokinase was contraindicated (duration of chest pain > 24 hours, peptic ulceration, recent surgery etc) were followed for up to one year. For these 26 patients, 10 ml of venous blood was taken at admission or immediately before treatment with streptokinase; within 24 hours of treatment or admission; on days 2–4; days 7, 14, and 28; and then at intervals of approximately 2, 4, 6, 8, 10 months, and one year after treatment (samples were usually taken within seven days of each time point after one month).

Enzyme linked immunosorbent assays were developed for IgG and the IgG1 subclass by the methods of Voller *et al.*[10] In brief, the wells of microtitre plates (Gibco, UK) were coated with 200 μl of 300 IU/ml of streptokinase (Kabivitrum Pharmaceuticals) in 0·05 mol/l carbonate/bicarbonate buffer (pH 9·5) and incubated for 16 hours at 4°C. The plate was then washed three times in phosphate

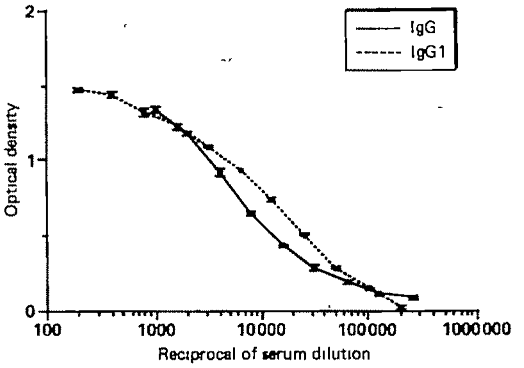


Figure 1 IgG standard curve (unbroken line) and IgG1 standard curve (dotted line) (1 SD) (n = 6). The vertical axis is the optical density of the colour change and the horizontal axis is the serum dilution on a logarithmic scale.

buffered saline with 0·01% Tween to remove any unbound antigen. Several dilutions of patient serum in the same buffer were then added to the wells and incubated for two hours at room temperature. The plates were again washed three times with buffer to remove unbound antibody. Horseradish peroxidase conjugated to sheep anti-human immunoglobulin (Immunodiagnostic Research Laboratory, University of Birmingham) was then added and incubated for a further two hours at room temperature. The plates were again washed to remove unbound antiglobulin, hydrogen peroxidase/*o*-phenylenediamine (Sigma, UK) in phosphate/citrate buffer (pH 5·0) was then added and the incubation was allowed to continue. When the colour change of a known positive standard on the plate reached a pre-determined value the reaction was stopped by the addition of 0·5 mol/l citric acid. The optical density of each well was read at 490 nm with a spectrophotometer (Dynatech Laboratories, UK).

Assays were devised to measure total IgG, IgG1, IgG2, IgG3, IgG4, and IgM. Standard IgG and IgG1 curves were generated from serum obtained from a patient who had been treated with streptokinase 10 days before (fig 1), and the IgM standard curve was generated from a known positive serum sample (kindly provided by Professor M Dykewicz, Department of Immunology, Northwestern University Medical School, Illinois, USA).

Results were expressed with reference to a fixed dilution on a standard curve that was included on every plate. This fixed titre was taken as a 1 in 6000 dilution of the standard serum for IgG and as a 1 in 4000 dilution for IgG1. The optical density value corresponding to the standard fixed dilution was obtained and the corresponding dilution giving the same optical density was derived from the dilution curve for each patient sample. The value obtained in this way from the patient dilution curve was taken as the result for that patient's serum. The reciprocal of the dilution was taken as the antibody titre (fig 2). Where undiluted patient serum did not achieve the optical density of the fixed standard plasma dilution the result was taken as zero for statistical purposes.

The validity of the assay was confirmed by pre-incubating pure streptokinase with positive serum in a separate experiment. When the sample was tested subsequently with the ELISAs a negative result was obtained.

The reproducibility of the assays was determined at the upper and lower ranges. For the low antibody titres we tested a patient's sample obtained before treatment. We tested within batch reproducibility by measuring the same sample six times on the same plate. At a mean IgG titre of 19 the within batch coefficient of variation (CV) was 14·7%. It was 12·7% for IgG1 (mean titre = 12). Between batch reproducibility was assessed by assaying the same sample six times on different days. The between batch CV was 29% for IgG and 31·8% for IgG1.

For the high titres the reproducibility was assessed by using a patient's sample obtained 14 days after streptokinase treatment. At a mean IgG titre of 4200 the within batch CV was 6·9% and the between batch CV was 12·9%. Results for IgG1 (mean titre = 1750) gave a within batch CV of 7·7% and between batch CV of 14·2%.

Total plasma IgG and IgM were assessed by single radial immunodiffusion[11 12] on prepoured plates (Binding Site, University of Birmingham) at presentation in the 20 patients followed after streptokinase therapy and the six patients who were not treated with streptokinase.

All results are expressed as mean (SE). The statistical significance of differences between patient groups and between daily data was determined by the Wilcoxon rank sum test for paired and unpaired data.

All patients gave informed consent and the study was approved by the local ethics committee.

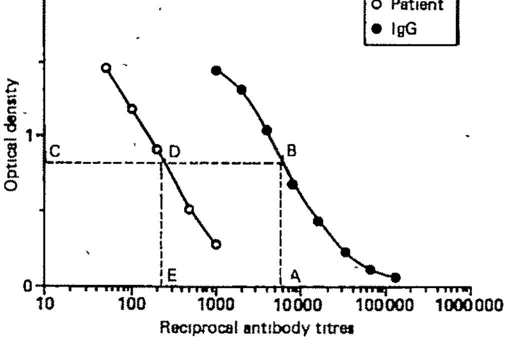


Figure 2 Method of obtaining result from a patient sample. The optical density results are shown for dilutions of a patient's sample (○) and standard sample (●). The optical density B–C is obtained for the fixed dilution of the standard serum (A) The point where line B–C transects the patient's sample dilution curve (D) is determined and the corresponding dilution (E) is taken as the result for the sample.

Results

Twelve of the 48 patients had no detectable IgG anti-streptokinase antibody before treatment. The remaining 36 patients had titres varying from 1 to 140. Figure 3 summarises the distribution of these titres.

Figure 4 shows the time course of the IgG response to intravenous streptokinase infusion in 20 patients. At presentation 16 of the patients had a detectable antibody titre (mean baseline titre for all 20 patients was 14·63 (4)). After infusion of streptokinase the titre showed a significant fall ($p = 0·003$) and became

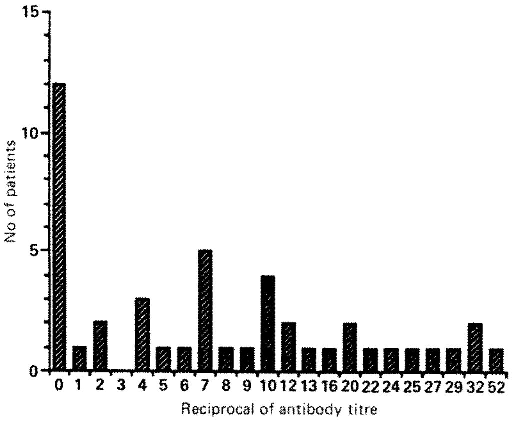


Figure 3 Distribution of baseline IgG titres of the 48 patients. The horizontal axis indicates the reciprocal of the antibody titre. The histograms indicate the number of patients (vertical axis) with that titre. Two patients were off the scale and had baseline titres of 80 and 140 respectively.

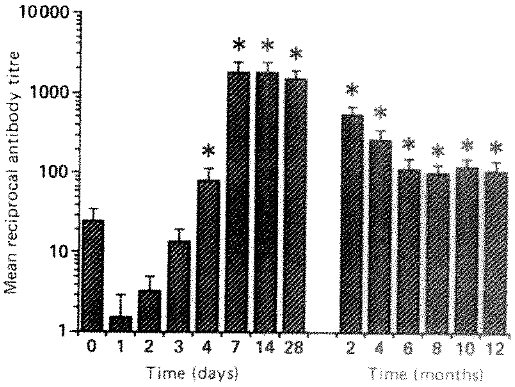


Figure 5 Time course (horizontal axis) of the IgG1 response (vertical axis) to intravenous streptokinase. Histograms are mean values and bars are 1 SE. All points indicated by asterisks are significantly higher than the baseline (day 0) values.

undetectable in 17 of the patients (mean titre 3 (2)). Subsequently there was a gradual increase and by day 4 the titre (91 (41)) was significantly higher than baseline concentrations ($p = 0\cdot018$). The titre increased further by day 7 reaching a peak on day 14 (mean titre 3192 (771) ($p < 0\cdot0001$)). Subsequently, the titre gradually declined, levelling off after about six months. However, by one year the mean titre (131 (36)) was still higher than the baseline value ($p < 0\cdot025$).

The pattern of IgG1 results resembled that for IgG. IgG1 titres were detectable in 13 patients (mean 26 (7)). Within 24 hours of treatment with streptokinase the titre decreased to 1 (1·47) ($p = 0\cdot003$). Subsequently it rose and it was significantly increased by day 4 (mean 79 (27) ($p = 0\cdot02$)). It reached a peak on day 14 (mean 1751 (589) ($p = 0\cdot0004$)) and declined to 107 (41) ($p < 0\cdot025$) by one year. Figure 5 summarises the results.

There was no evidence of IgG2, IgG3, or IgG4 antibodies to streptokinase and only low titres of IgM (< 1/30) which did not alter over the period of the study.

There was a large variation in the antibody response. Though the baseline titres were relatively similar for all patients, peak titres for IgG varied from 140 to 10 000, and two patients had peak titres of < 200. However, even these patients showed no IgM antibody response to streptokinase even though total IgM and IgG were normal.

The six control patients who did not receive streptokinase had a mean baseline IgG titre of 10 (5) which was similar to that of the patients who received the drug. This titre did not change in the 28 days after the infarct (day 1 = 14 (7); day 4 = 11 (6); day 14 = 19 (5); day 28 = 16 (5)). Nor was there any change in IgG1 antibody titre over the same period.

Total IgG and IgM results were normal for all patients (mean total IgG concentrations = 9355 (953) mg/l; IgG range 1400–16400 mg/l; mean total IgM = 1739 mg/l (210); IgM range 525–2540 mg/l).

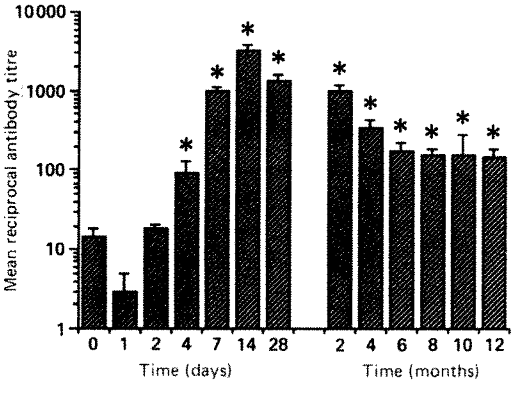


Figure 4 Time course (horizontal axis) of the IgG response (vertical axis) to intravenous streptokinase. Histograms are mean values and bars are 1 SE. All points indicated by asterisks are significantly higher than the baseline (day 0) value.

Discussion

The purpose of this study was to assess the presence and nature of streptokinase antibodies and their response to an intravenous infusion of streptokinase.

Most of the patients (75%) had detectable IgG and IgG1 antibody titres to streptokinase at presentation. The values were relatively low, but they indicate that such antibodies are widespread in the population, presumably as a result of streptococcal infection (none of our patients had been treated previously with streptokinase).

The antibody titres fell within 24 hours of treatment presumably because of combination between the antibody and antigen, streptokinase. Thereafter, the antibody titres increased gradually; they were significantly raised four days after treatment. The titres reached a peak after 14 days and subsequently declined but they had still not returned to baseline values after one year.

This pattern of immunoglobulin change suggests a secondary immune response. The antibodies found both at presentation and in the subsequent response were IgG and of the IgG1 subclass as predicted for a protein antigen such as streptokinase.[13] This pattern of response and the absence of a rise in IgM titre indicate that this is a secondary rather than a primary immune response. The six control patients showed no significant change in titre, again indicating that the antibody response was specific to streptokinase treatment.

Peak antibody titres to streptokinase varied considerably among patients (from 140–10 000 for IgG) with two patients showing only a slight rise (140 and 175) respectively). We do not known whether this represents an extreme end of the normal range or whether these two subjects have an isolated immune deficiency against protein antigens. Certainly they had no history of recurrent infections. Further studies of their response to other protein or polysaccharide antigens, however, would be needed to rule out this possibility..

The time course of the secondary immune response seen here resembles that described by Jalihal *et al* "for streptokinase neutralising capacity",[14] indicating that the neutralisation is probably due to antibody. Jalihal *et al* suggested that the streptokinase dose should be titrated to overcome this neutralising capacity in patients in whom it is high. Our study suggests that if antibody is responsible for neutralisation, the dose would need to be increased if a patient presented with a second myocardial infarction within one year of the initial treatment. The administration of an increased dose of streptokinase within this period could lead to an immune reaction as well as a failure to achieve an adequate thrombolytic state. However, this possibility remains theoretical at present and further studies will be required to clarify the role and implications of these antibodies. Nevertheless, until their role has been clarified, it would be prudent to avoid repeating the dose between three days and at least one year after the initial therapy. During this period an alternative non-streptokinase thrombolytic agent could be used.

1 ISIS (Second International Study of Infarct Survival). Collaborative Group. Randomised trial of intravenous streptokinase, oral aspirin, both or neither among 17 187 cases of suspected acute myocardial infarction. *Lancet* 1988;**ii**:349–60.

2 Italian Group for the study of streptokinase in myocardial infarction (GISSI). Effectiveness of intravenous thrombolytic treatment in acute myocardial infarction. *Lancet* 1986;**i**:397–401.

3 James DCO. Anti-streptokinase levels in various hospital patient groups. *Postgrad Med J* 1973;(Aug suppl):26–9.

4 Fletcher AP, Alkjaersig N, Sherry S. The maintenance of a sustained thrombolytic state in man. 1. Induction and effects. *J Clin Invest* 1959;**38**:1111–9.

5 McGrath KG, Zeffren B, Alexander J, Kaplan K, Patterson R. Allergic reactions to streptokinase consistent with anaphylactic or antigen antibody complex mediated damage. *J Allergy Clin Immunol* 1984;**76**(3):453–7.

6 Alexopoulos D, Raine AE, Cobbe SM. Serum sickness complicating intravenous streptokinase therapy in acute myocardial infarction. *Eur Heart J* 1984;**5**:1010–2.

7 Totty WG, Romano T, Benian GM, Gilula LA, Sherman LA. Serum sickness following streptokinase therapy. *Am J Roentgenol* 1981;**138**:363–73.

8 Taylor C, Weatherbee TC, Esterbrooks DJ, Katz DA, Aronow WS, Kenik JG, *et al* Serum sickness following selective intracoronary streptokinase. *Current Therapeutic Research* 1984;**35**:433–8.

9 McGrath K, Patterson R. Immunology of streptokinase in human subjects. *Clin Exp Immunol* 1985;**62**:421–6.

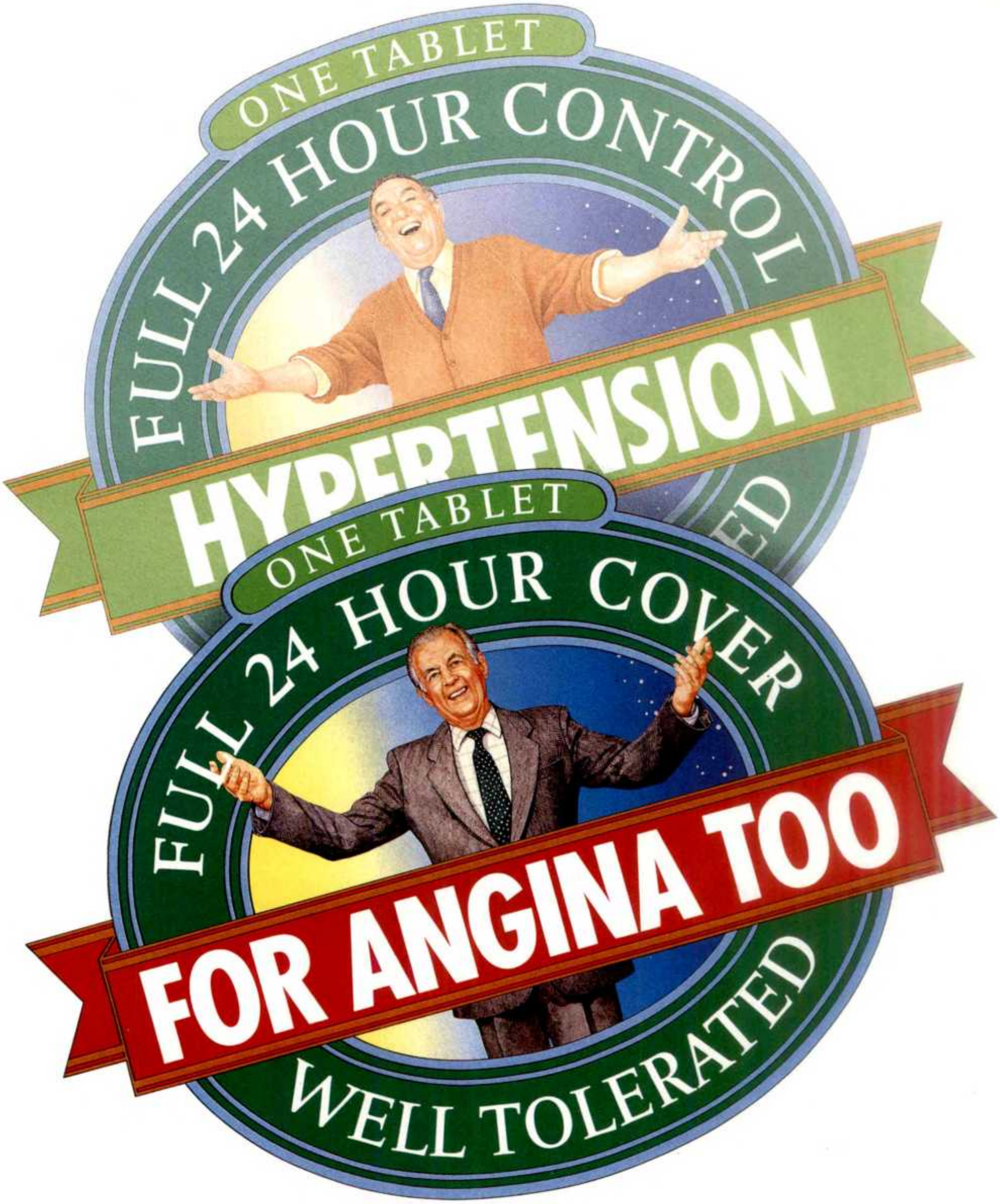
10 Voller A, Bidwell DE, Bartlett A. Enzyme immunoassays in diagnostic medicine. Theory and practice. *Bull World Health Organ* 1976;**76**:53–65.

11 Mancini G, Carbonara AO, Heremans JF. Immunochemical quantitation of antigens by single radial immunodiffusion. *Immunochemistry* 1965;**2**:235–54.

12 Fahey JL, McKelvey EM. Quantitative determination of serum immunoglobulins in antibody agar plates. *J Immunol* 1965;**94**:84–90.

13 Stevens R, Dichek D, Keld B, Heiner D. IgG1 is the predominant subclass of in vivo and in vitro produced anti-tetanus toxoid antibodies and also serves as the membrane IgG molecule for delivering inhibitory signals to anti-tetanus toxoid antibody producing B cells. *J Clin Immunol* 1983;**3**(1):65–9.

14 Jalihal S, Morris GK. Antistreptokinase titres after intravenous streptokinase. *Lancet* 1990;**335**:184–5.



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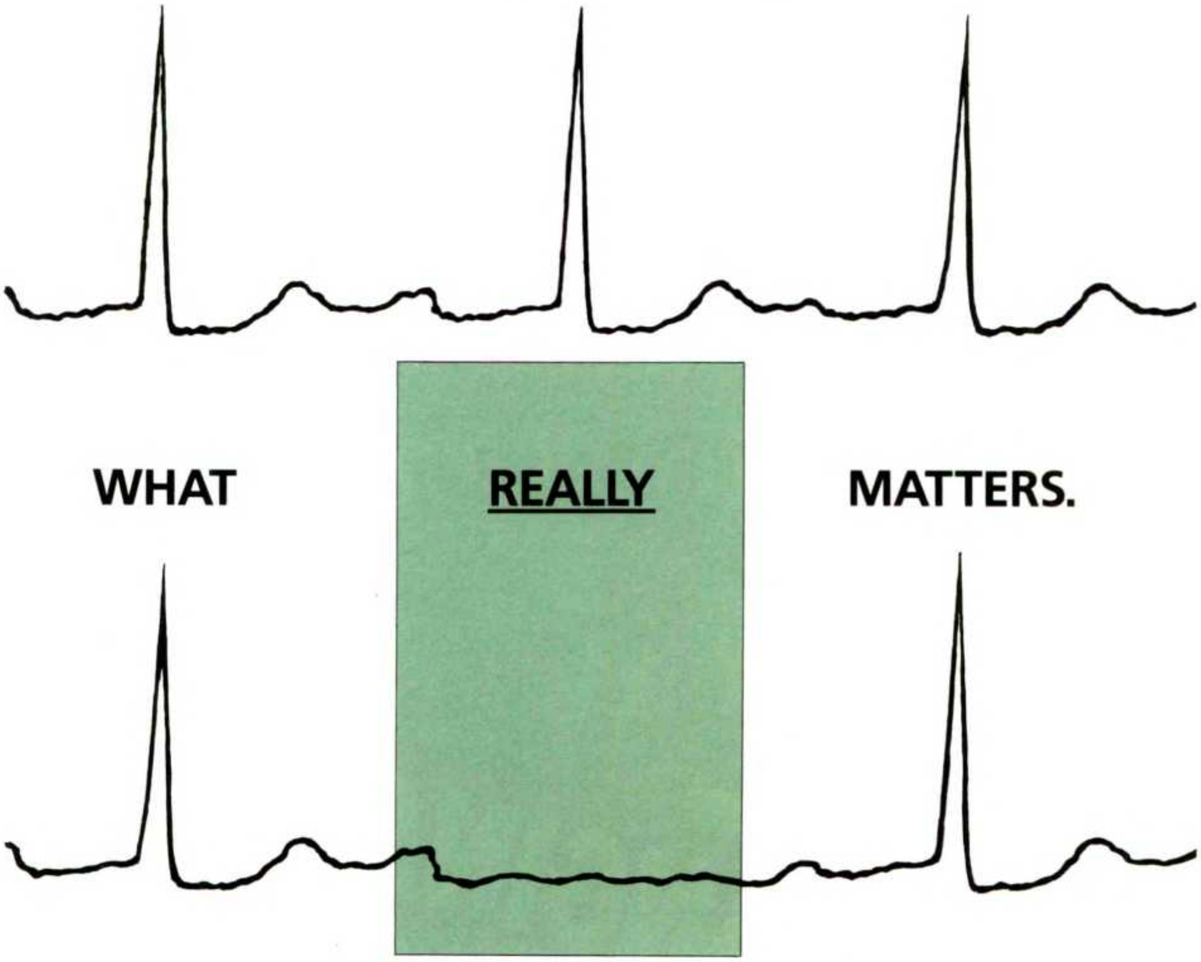

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Predictive value of ventricular arrhythmias for patency of the infarct-related coronary artery after thrombolytic therapy

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Abstract

In animal studies reperfusion of coronary arteries is commonly accompanied by ventricular arrhythmias. It is not certain, however, whether ventricular arrhythmias can be used as a reliable non-invasive marker of reperfusion in humans. Two-channel Holter recordings were obtained from the start of an intravenous infusion of streptokinase until coronary angiography (2·8 (2·7) hours (mean (SD)) afterwards) in 57 patients with acute myocardial infarction of less than four hours who were generally not treated with anti-arrhythmic drugs. Ventricular arrhythmias occurred in 21 (37%) of the 57 patients: accelerated idioventricular rhythm in 13 patients and non-sustained ventricular tachycardia in 15 patients. Seven patients had both accelerated idioventricular rhythm and non-sustained ventricular tachycardia. Coronary angiography showed a patent infarct-related vessel in 12 (92%) of the 13 patients with accelerated idioventricular rhythm (95% confidence interval 66 to 99%), in 22 (50%) of the 44 patients without accelerated idioventricular rhythm (95% CI 34 to 66%), in 11 (73%) of the 15 patients with non-sustained ventricular tachycardia (95% CI 45 to 92%), and in 23 (55%) (95% CI 39 to 71%) of the 42 patients who did not have non-sustained ventricular tachycardia. Seventeen (81%) of the 21 patients with accelerated idioventricular rhythm, or non-sustained ventricular tachycardia, or both, had a patent infarct-related vessel (95% CI 58 to 94%) as did 17 (47%) of the 36 patients with no ventricular arrhythmia (95% CI 29 to 65%).

In patients with accelerated idioventricular rhythm after thrombolysis the infarct-related vessel is almost certain to be patent; but the infarct-related coronary artery can still be patent when no arrhythmia is seen.

Because intravenous thrombolytic agents are increasingly used to treat acute myocardial infarction non-invasively determined indices of reperfusion are needed.[1] Ventricular arrhythmias are regarded as a reliable sign of reperfusion in most, but not all, laboratory animals.[2–6] In humans, however, some of the arrhythmias seen in the first hours after the onset of infarction can be attributed to the inherent electrical instability of the ischaemic myocardium and not to reperfusion. To investigate the difference between "infarction arrhythmias" and "reperfusion arrhythmias", we need to measure the patency rate of the infarct-related coronary artery and disorders of the heart rhythm within a well-defined interval.

We therefore determined the predictive value of ventricular arrhythmias for patency of the infarct-related vessel in patients with acute transmural infarction by monitoring the heart rhythm with Holter recording from the start of streptokinase administration until angiographic visualisation of the infarct-related vessel up to four hours later (that is, the study period).

Patients and methods

PATIENTS

Fifty seven patients with acute myocardial infarction were treated with intravenous streptokinase. We studied male and female patients below the age of 71 years with symptoms of acute myocardial infarction for less than four hours and ST segment elevation of $\geqslant 1$ mm in at least two leads of the standard 12 lead electrocardiogram. We excluded patients with a history of abnormal bleeding, use of anticoagulant drugs, recent surgery (<2 weeks), previous cerebral haemorrhage or injury, impaired renal function (serum creatinine concentration >300 μmol/l), systolic blood pressure >200 mm Hg, diastolic >120 mm Hg, severe heart failure with pulmonary congestion on admission, any malignancy (except those of the skin), or previous treatment with streptokinase.

All patients were informed of the treatment and its potential risks and were asked for consent. β Blockers were used on the day before or on the day of admission by 10 patients and calcium antagonists by six patients. During the study period 10 patients were treated with atropine for bradycardia or atrioventricular conduction disturbances. Lignocaine was given to five patients, in two by continuous infusion after an episode of ventricular fibrillation before admission to the coronary care unit. In the three other patients lignocaine was given as a bolus injection at home by the general practitioner for unknown reasons, probably extrasystoles.

TREATMENT

Twenty patients were treated as part of a dose-ranging trial of streptokinase,[7] in which they received a one hour infusion of 200 000 IU (n = 4), 750 000 IU (n = 6), 1 500 000 IU (n = 5), or 3 000 000 IU (n = 5) of streptokinase (Kabikinase). Twenty four other patients were treated with 1 500 000 IU of intravenous streptokinase plus oral or intravenous captopril (Capoten) in an attempt to diminish reperfusion damage of the myocardium, as described elsewhere.[8] Thirteen other patients were given 1 500 000 IU of intravenous streptokinase only. The infusion was stopped if allergic reactions, bleeding complications, or a fall in blood pressure developed. Steroids, antiarrhythmic drugs, or salicylates were not used routinely. Analgesic drugs and nitrates were given freely. Coronary angiography was performed within four hours of the streptokinase infusion.

CORONARY ANGIOGRAPHY

Coronary cineangiography was performed by the Judkins approach. Immediately after the introduction of a sheath in the femoral artery, patients were given 5000 IU of heparin. Furthermore, each patient was treated with 2·5 mg isosorbide dinitrate sublingually. The right coronary artery was usually filmed in two projections and the left coronary artery in at least three views. All coronary angiograms were independently analysed by cardiologists who specialised in coronary angiography. The perfusion of the infarct-related vessel was classified according to the thrombolysis in myocardial infarction (TIMI) study group[9]: patency was defined as TIMI perfusion class II or III.

HOLTER RECORDINGS

A two-channel Holter recorder was connected to the patient immediately on admission. Soon after infusion of streptokinase began. Recording continued until angiography of the infarct-related vessel was completed. All recordings were manually analysed on a beat-to-beat basis (paper speed 25 mm/s) by one experienced cardiologist (JHL) and all arrhythmias detected were recorded on paper.

DEFINITIONS OF ARRHYTHMIAS

Accelerated idioventricular rhythm was defined as the occurrence of at least three consecutive uniform complexes of ventricular origin with a frequency of 60 to 100 beats/minute. Non-sustained ventricular tachycardia was defined as at least three consecutive ventricular complexes with a frequency of more than 100 beats/minute, for <30 seconds. Sustained ventricular tachycardia was defined as a ventricular tachycardia lasting 30 seconds or more.

STATISTICAL ANALYSIS

Continuous distributed values are given as the mean (SD). Sensitivity was defined as the percentage of patients with an open vessel with the rhythm disturbance under examination; specificity was defined as the percentage of patients with an occluded vessel who did not have that rhythm disturbance. The results are given with 95% confidence intervals.[10]

Results

Table 1 shows the characteristics of patients with various rhythm disturbances. Ventricular arrhythmias occurred in 37% (21/57) of the patients: accelerated idioventricular rhythm in 13 patients and non-sustained ventricular tachycardia in 15 patients. Both accelerated idioventricular rhythm and non-sustained ventricular tachycardia occurred in seven patients. Sustained ventricular tachycardia and ventricular fibrillation were never recorded.

Patency of the infarct-related vessel was seen in 92% (12/13) of patients with accelerated idioventricular rhythm and 50% (22/44) of those without; and in 73% (11/15) of the patients with non-sustained ventricular tachycardia and 55% (23/42) of those without ventricular tachycardia. The infarct-related vessel was patent in 81% (17/21) of the patients with accelerated idioventricular rhythm or non-sustained ventricular tachycardia or both. Forty seven per cent (17/36) of patients without ventricular arrhythmia had patent vessels. Six of the seven (86%) patients who had both accelerated idioventricular rhythm and non-sustained ventricular tachycardia had patent vessels.

Both patients who had an episode of ventricular fibrillation before admission to the hospital had patent infarct-related coronary arteries as did 70% (7/10) of patients who were treated with atropine for bradycardia. In those without bradycardia, patency was seen in 57% (27/47).

Table 2 shows the sensitivity, specificity, and the predictive value of the occurrence of various rhythm disturbances for patency.

Table 1 Characteristics and incidence of ventricular arrhythmias in 57 patients who were treated with intravenous streptokinase for acute myocardial infarction

	AIVR	*ns-VT*	*AIVR, ns-VT, or both*	*AIVR and ns-VT*	*No arrhythmias*	*All patients*
Number	13	15	21	7	36	57
Age (yr)	54·6 (10·8)	54·1 (8·7)	54·3 (9·4)	54·4 (9·3)	55·8 (11·7)	55·6 (9·7)
Male (%)	76	88	81	71	83	81
Anterior wall infarction (%)	54	44	48	57	50	49
Duration of symptoms (min)	151 (54)	148 (59)	150 (56)	143 (88)	143 (48)	146 (50)
Interval between SK infusion and rhythm disturbance (min)	105 (74)	98 (75)	101 (75)	77 (56)		
Patency (%)	92	73	81	86	50	60

AIVR, accelerated idioventricular rhythm; ns-VT, non-sustained ventricular tachycardia; SK, streptokinase

Table 2 Sensitivity, specificity, and predictive values of the occurrence of various rhythm disturbances for patency of the infarct-related coronary artery of 57 patients, of whom 34 had a patent vessel (numbers in parentheses are 95% confidence intervals)

Arrhythmia	*Number of patients with rhythm disturbances*	*Sensitivity (%)*	*Specificity (%)*	*Predictive value of positive test (%)*	*Predictive value of negative test (%)*
AIVR	13	35 (20 to 52)	96 (78 to 99)	92 (66 to 99)	50 (34 to 66)
Non-sustained VT	15	32 (18 to 50)	83 (62 to 95)	73 (45 to 92)	45 (29 to 61)
AIVR or non-sustained VT or both	21	50 (32 to 68)	83 (62 to 95)	81 (58 to 94)	53 (35 to 71)
AIVR and non-sustained VT	7	18 (7 to 34)	96 (78 to 99)	86 (54 to 99)	44 (30 to 59)
Ventricular fibrillation	2	6 (1 to 19)	100 (86 to 100)	100 —	42 (28 to 56)
Bradycardia	10	21 (9 to 37)	87 (67 to 97)	70 (35 to 93)	43 (28 to 58)

AIVR, accelerated idioventricular rhythm; VT, ventricular tachycardia.

Discussion

Necrosis and/or ischaemia of myocardial cells may initiate abnormal ventricular depolarisations which are currently thought to be triggered by reentry or triggered activity.[11-15] Ventricular rhythm disturbances, however, may also be caused by reperfusion and in such cases reentry or enhanced automaticity may play a role.[16]

REPERFUSION ARRHYTHMIAS IN ANIMALS

An interesting aspect of reperfusion arrhythmias is the existence of an apparent species specificity. In some laboratory animals the occurrence of arrhythmias can be considered as a reliable non-invasive sign of reperfusion.[2-6] Ventricular tachycardias and fibrillation are often seen in dogs,[4 6] pigs, and rats[3] immediately after reperfusion, though this is less common in cats.[2 5]

REPERFUSION ARRHYTHMIAS IN HUMANS

We obtained Holter recordings in a well-defined period of the acute infarction: from shortly before the start of thrombolytic therapy to the primary end point of the study (the injection of contrast agent into the infarct-related coronary artery). We emphasise that our patients were generally not treated with antiarrhythmic drugs. It seemed that accelerated idioventricular rhythm gave the highest scores in predicting the outcome of angiography. Accelerated idioventricular rhythm predicted patency in 92% of patients; but on the other hand, its absence predicted a permanent occlusion in only 50%. So this arrhythmia has a very high specificity (96%) and a poor sensitivity (35%) as a non-invasive index of patency. It should also be noted that coronary angiography is only a "snapshot"; it does not exclude intermittent occlusion and recanalisation.[17] None the less, it is the best diagnostic tool for recording the coronary anatomy that is clinically available.

Sustained ventricular tachycardia or ventricular fibrillation did not occur during the period of investigation. However, before the period of investigation two patients with patent vessels had ventricular fibrillation, which suggests that there may be a relation between the occurrence of ventricular fibrillation and patency, but this sample size is too small to draw any conclusions.

Non-sustained ventricular tachycardia was slightly more common than accelerated idioventricular rhythm (15 patients *v* 13 patients, respectively), but non-sustained ventricular tachycardia has both a poorer specificity (83%) and sensitivity (32%) than does accelerated idioventricular rhythm.

COMPARISON WITH OTHER STUDIES

Large controlled trials showed that life threatening arrhythmias were less common in patients after thrombolytic therapy than in control groups.[18-20] Furthermore, Theroux and coworkers showed that the number of ventricular extrasystoles per hour during the first 24 hours of infarction was significantly less after thrombolysis than after conservative treatment.[21]

Arrhythmias during intracoronary streptokinase administration in humans have been described (specifically) in three studies,[22-24] which, unfortunately, are difficult studies to compare for the following reasons. First, the definition of "reperfusion arrhythmias" differed from study to study. Secondly, in such a type of investigation, arrhythmias that were less relevant to the course of action in the coronary care unit (such as accelerated idioventricular rhythm) were often ignored. For instance, in our study, we found that the routine records of rhythm kept by the nursing staff were not complete: seven of the 13 episodes of accelerated idioventricular rhythm that were found on the Holter recordings were not recorded. This may partly explain why other studies did not show that rhythm disturbances in routine rhythm strip recordings were predictive for patency.[1] Thirdly, the incidence of reperfusion arrhythmias may be different with intracoronary and intravenous streptokinase administration. Also, routine administration of antiarrhythmic drugs may influence the incidence of arrhythmias; indeed in the studies described by Goldberg *et al* and Miller *et al* patients were routinely treated with lignocaine.[22 23]

TIME OF REPERFUSION

Animal studies showed that arrhythmias occur at the time of reperfusion. So rhythm recordings can be used to calculate the interval from the onset of symptoms until reperfusion. This is a non-invasive method of calculating the total period of tissue anoxia. Such information may be of great value when the effects of thrombolytic drugs administered at different rates of infusion are compared. It cannot be obtained by angiography or other non-invasive methods such as enzyme studies.[25]

CLINICAL IMPLICATIONS

In view of the results of the TIMI II study of the therapeutic strategy after thrombolytic therapy, does information on patency have any practical consequence?[26] There were no clear benefits with either invasive or conservative management of patients after thrombolytic therapy, regardless of whether or not recanalisation was achieved. Nevertheless, the presence of accelerated idioventricular rhythm is highly predictive of patency and easy to record. This may make it a useful method for calculating the total anoxia period, so it seems sensible to instruct the nursing staff on the importance of this arrhythmia.

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1 Califf RM, O'Neil W, Stack RS, *et al* TAMI Study Group. Failure of simple clinical measurements to predict perfusion status after intravenous thrombolysis *Ann Intern Med* 1988;108:658–62.

2 Zuanetti G, Vanoli E, Zaza A, Priori S, Stromba-Badiale M. Schwartz PJ. Lack of correlation between occlusion and reperfusion arrhythmias in the cat. *Am Heart J* 1985; 109:932–6.

3 van Gilst WH, de Graeff PA, Kingma JH, Wesseling H, de Langen CDJ Captopril reduces purine loss and reperfusion arrhythmias in the rat heart after coronary artery occlusion *Eur J Pharmacol* 1984,110 113–7

4 Sheehan FH, Epstein SE Effects of calcium channel blocking agents on reperfusion arrhythmias. *Am Heart J* 1982; 103 973–7

5 Pogwizd SM, Corr PB Electrophysiologic mechanisms underlying arrhythmias due to reperfusion of ischemic myocardium *Circulation* 1987,76.404–26.

6 Bolli R, Patel B Factors that determine the occurrence of reperfusion arrhythmias. *Am Heart J* 1988;115 20–9

7 Six AJ, Louwerenburg HW, Braams R, *et al* A double-blind randomized multicenter dose-ranging trial of intravenous streptokinase in acute myocardial infarction. *Am J Cardiol* 1990,65·119–23.

8 Kingma JH, Louwerenburg JW, Six AJ, van Gilst WH, de Graeff PA, Wesseling H. Concomitant use of captopril during thrombolytic therapy in acute myocardial infarction In Sonnenblick EH, Laragh JH, Lesh M, eds. *New frontiers in cardiovascular therapy: focus on angiotensin converting enzyme inhibition*. Princeton Excerpta Medica, 1989.277–85.

9 Sheehan FH, Braunwald E, Canner P, *et al* The effect of intravenous thrombolytic therapy on left ventricular function. a report on tissue-type plasminogen activator and streptokinase from the Thrombolysis in Myocardial Infarction (TIMI phase I) trial. *Circulation* 1987;75. 817–29

10 Steel RGD, Torrie JH *Principles and procedures of statistics.* New York· McGraw Hill, 1960.table A14A on page 454.

11 Janse MJ, Kleber AG. Electrophysiological changes and ventricular arrhythmias in the early phase of regional myocardial ischaemia. *Circ Res* 1981,49:1069–81.

12 Janse MJ, Capelle FJL, Morsink H, *et al*. Flow of "injury" current and patterns of excitation during early ventricular arrhythmias in acute regional myocardial ischaemia in isolated porcine and canine hearts Evidence for two different arrhythmogenic mechanisms *Circ Res* 1980, 47.151–65.

13 van Hemel NM, Swenne CA, Robles de Medina EO. Assessment of mechanisms of ventricular arrhythmias from the surface electrocardiogram in 118 patients *Eur Heart J* 1987,8:813–20.

14 Manning AS, Hearse DJ Reperfusion-induced arrhythmias: mechanisms and prevention. *J Mol Cell Cardiol* 1984,16·497–518.

15 Hoffman B, Rosen M. Cellular mechanisms for cardiac arrhythmias *Circ Res* 1981,49.1–15.

16 Manning AS, Hearse DJ. Reperfusion-induced arrhythmias mechanism and prevention. *J Mol Cell Cardiol* 1984; 16 497–518.

17 Hackett D, Davies G, Chierchia S, Maseri A Intermittent coronary occlusion in acute myocardial infarction *N Engl J Med* 1987;317:1055–9.

18 GISSI Effectiveness of intravenous thrombolytic treatment in acute myocardial infarction *Lancet* 1986;i 397–402.

19 ISAM study group A prospective trial of intravenous streptokinase in acute myocardial infarction *N Engl J Med* 1986;314 1465–71.

20 Simoons ML, Serruys PW, van den Brand M, *et al*. Improved survival after early thrombolysis in acute myocardial infarction *Lancet* 1985;ii.578–81

21 Theroux P, Morisette D, Juneau M, de Guise P, Pelletier G, Waters DD. Influence of fibrinolysis and percutaneous transluminal coronary angioplasty on the frequency of ventricular premature complexes *Am J Cardiol* 1989; 63:797–801.

22 Goldberg S, Greenspon AJ, Urban PL, *et al*. Reperfusion arrhythmia. a marker of restoration of antegrade flow during intracoronary thrombolysis for acute myocardial infarction. *Am Heart J* 1983,105·26–32

23 Miller FC, Krocoff MW, Satler LF, *et al*. Ventricular arrhythmias during reperfusion *Am Heart J* 1986;112: 928–32

24 Kuck KH, Schofer J, Schluter M, Bleifeld W, Mathey D. Reperfusion arrhythmias in man: influence of intravenous lidocaine *Eur Heart J* 1985;6(suppl E) 163–7.

25 Katus HA, Diederich KW, Scheffold T, Uellner M, Schwarz F, Kubler W. Noninvasive assessment of infarct reperfusion. the predictive power of the time to peak value of myoglobin, CKMB, and CK in serum *Eur Heart J* 1988;9.619–24.

26 The TIMI Study Group Comparison of invasive and conservative strategies after treatment with intravenous tissue plasminogen activator in acute myocardial infarction *N Engl J Med* 1989;320 618–27.

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Post-prandial worsening of angina: All due to changes in cardiac output?

A J Cowley, L J Fullwood, K Stainer, E Harrison, A F Muller, J R Hampton

Abstract

***Background*—The precise mechanism leading to the post-prandial worsening of angina has yet to be adequately defined. It has been attributed to an increase in double product but is perhaps more likely to be related to an increase in cardiac output after food. This study was designed to evaluate the effects of food on patients' exercise tolerance and compare these with changes in haemodynamic variables.**

***Methods*—23 patients with chronic stable angina who had post-prandial worsening of their angina were studied. The patients were evaluated on two occasions and at each visit they underwent two symptom limited treadmill exercise tests. They remained fasting on the first visit and were given a 1400 kcal meal 60 minutes before the second exercise test on the second visit. Time to onset of 1 mm ST segment depression, heart rate, systemic arterial blood pressure, and cardiac output were measured at rest and during exercise.**

***Results*—There were no differences in any of the variables during the two exercise tests on the day the patients remained fasting. After the meal exercise tolerance fell significantly by 136 seconds and the stage at which 1 mm ST segment depression was first seen was also significantly reduced. Resting cardiac output increased significantly by 0·86 l/min with the patients sitting and by 0·89 l/min standing. The exercise times after food were significantly related to cardiac output even when fasting times were taken into account. Resting heart rate increased significantly by 8·3 beats per minute sitting and 10·4 beats per minute standing. There was little change in blood pressure and no evidence that the double product predicted the post-prandial exercise time.**

***Conclusions*—Worsening of angina was related to the increase in cardiac output after a meal and successful treatment will depend upon the prevention of this increase.**

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The observation that eating can worsen angina was first made over two centuries ago.[1] However, it has been surprisingly difficult to demonstrate the mechanism by which this occurs. Intuitively it might be expected that a meal causes an increase in cardiac output and that this accounts for the worsening of symptoms, but it has been almost universally impossible to show this with invasive techniques and in most studies there has been no consistent increase in cardiac output post-prandially.[2 3] Post-prandial deterioration in angina has therefore been attributed to an increase in heart rate and blood pressure which is taken to indicate an increase in myocardial oxygen demand.[4] Even the consistency of these changes is in doubt because simple non-invasive measurements showed that food causes a reduction in blood pressure and little if any increase in heart rate in elderly subjects, who are those most likely to have angina.[5] The difficulty in defining adequately the mechanism of post-prandial worsening of angina therefore seems to be attributable to the invasive nature of the techniques used.

We showed that cardiac output can be measured non-invasively and reliably by analysis of respiratory gases[6] and that a modest meal increased the cardiac output of a group of normal subjects.[7] If methodological problems are the reason for the difficulties in showing the cause of post-prandial angina then use of a non-invasive technique may overcome these. The purpose of this study was to evaluate quantitatively the effect of food on the exercise tolerance of patients with angina and to try to determine the relevance of haemodynamic changes to any deterioration in angina.

Patients and methods

Twenty three patients with chronic stable angina participated in the study. All described a worsening of their angina after meals. Twenty one were men and the patients were aged 46–69 years. All were limited by angina on treadmill exercise testing. Antianginal medication was stopped, in those patients taking prophylactic treatment, at least 24 hours before each exercise test except for sublingual glyceryl trinitrate which was permitted up to two hours before treadmill exercise testing.

All patients were fully familiarised with the study protocol on at least two occasions before entering the study. They were asked to attend the exercise laboratory at 11 am on two days one week apart having fasted from midnight. On each visit they underwent two symptom limited exercise tests separated by at least 120 minutes. On the first (control) day the patients remained fasting and after the first test on the second (test) day they were given a standard meal of 1400 kcal to be eaten 60 minutes before the second test.

TREADMILL EXERCISE TESTS

All patients exercised to a symptom limited maximum with a modified low level Bruce protocol. The speed and slope of the treadmill were increased after three minutes at each of the following stages:

	I	*II*	*III*	*IV*	*V*	*VI*
Speed (km/h)	2·7	2·7	2·7	2·7	4·0	5·4
Slope (°)	0	1·3	2·6	4·3	5·4	6·3

The exercise stages were prolonged to four minutes during stages I and III to enable cardiac output to be measured.

Heart rate was recorded at rest and at the end of each stage of exercise. Blood pressure was measured by auscultation with a sphygmomanometer at rest and at the end of each stage of exercise. Standard 12 lead electrocardiograms were recorded at rest and every three minutes during the treadmill test and at the end of exercise.

Time to onset of 1 mm ST segment depression in any lead from the 12 lead electrocardiogram was measured in those patients who had changes in all four tests.

CARDIAC OUTPUT

We measured cardiac output by an indirect Fick principle by monitoring respiratory gases with a mass spectrometer (V G Medicals). Carbon dioxide was used as the indicator. Carbon dioxide production was calculated from minute ventilation and mixed expired carbon dioxide concentration, the partial pressure of carbon dioxide in pulmonary venous (systemic arterial) blood was derived from end tidal carbon dioxide concentration, and the partial pressure in mixed venous blood was measured after a rebreathing manoeuvre. These three variables were used to solve the Fick equation.

Cardiac output was measured with the patients sitting, standing, and at fixed submaximal workloads at the end of stages I and III during the treadmill exercise test. The coefficient of variation of the method was 8·2%.

STATISTICAL ANALYSIS

The effect of visit (week 1 compared with week 2) and exercise test (first compared with second) on maximal exercise duration and each of the haemodynamic measurements was assessed by a three factor analysis of variance with patient identity included as a blocking factor.[8] We used the statistical modelling package *GLIM*.[9] In each case the magnitude of the variable associated with the first order interaction term involving the factors visit and exercise, gives a measure of the effect of the meal.

The time to onset of 1 mm ST segment depression was coded according to the stage at which it first occurred. Patients who stopped exercising without this degree of ST depression developing were coded as stage VII—that is, beyond the end of exercise. The within visit difference in score (between the second and first exercise test) was calculated to give a measure of the effect of repeated exercise (visit 1) and the additional effect of the meal (visit 2). The difference between the visit differences can therefore be interpreted as a measure of the effect of the meal. We examined these with a Wilcoxon signed rank test.

The relation between cardiac output and maximal exercise time was investigated by multiple regression techniques. Specifically, a regression model was fitted that related exercise time after the meal to the exercise time before the meal. Change in cardiac output was then added to this regression to see whether this additional information improved the prediction of exercise time after the meal.

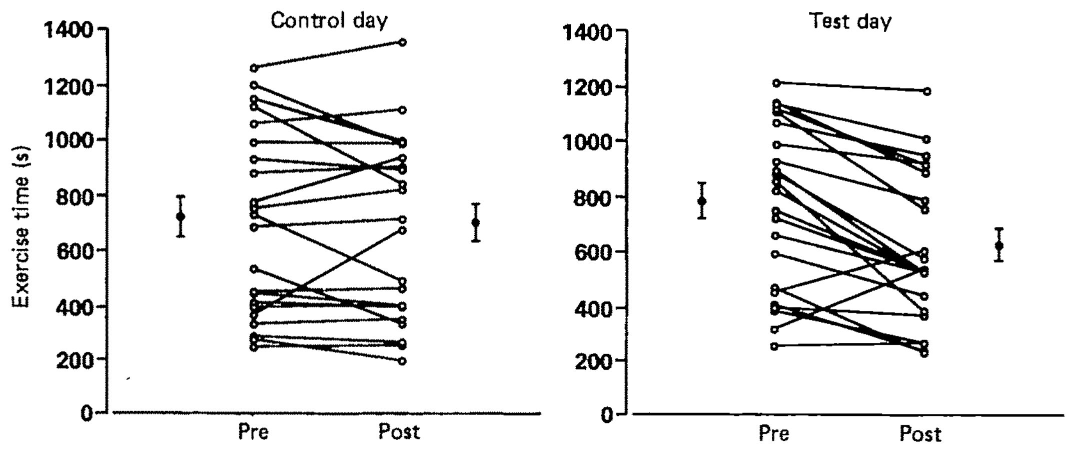
Results

All the patients had moderate angina and when they were studied they were not taking medication. Three patients were unable to complete stage I of the protocol on at least one occasion and seven could not complete stage II for all four tests.

SYMPTOM LIMITED EXERCISE TOLERANCE

Figure 1 shows the exercise tolerance of the patients on the control and study days. On the

Figure 1 Individual and mean (SEM) values for the symptom limited exercise tolerance of the patients on the control and test days (p < 0·01 on the test day).



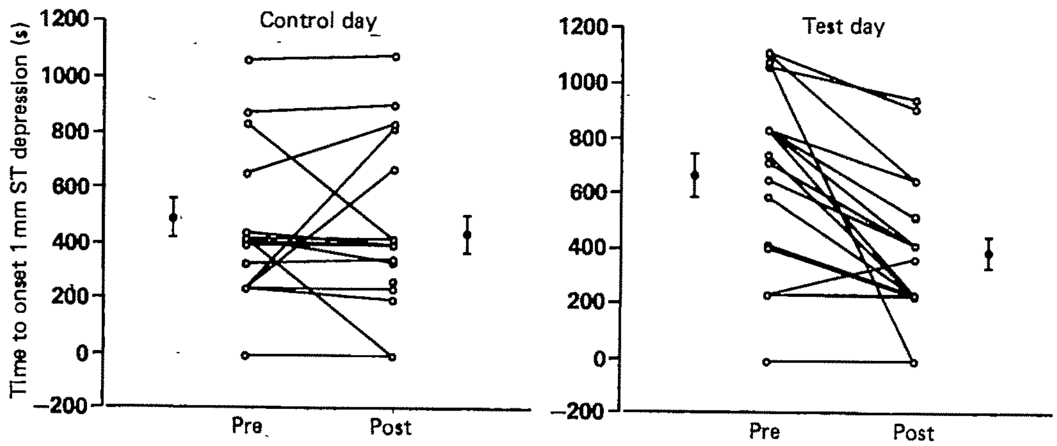


Figure 2 Individual and mean (SEM) values for time to onset of 1 mm ST segment depression in those patients in whom this occurred on the control and test days (p < 0·05 on the test day).

control day 11 patients had greater exercise times on the second exercise test compared with only three patients on the test day. The mean (SEM) times for the control day were 725 (70) seconds for the first test and 703 (69) seconds for the second test. On the test day the times were 783 (65) and 626 (59) seconds. Therefore on the control day there was a small decrease in exercise time for the second test which may indicate the effects of repeated testing to a symptom limited maximum. When this was taken into account with analysis of variance the effect of the meal was to reduce exercise time by 136 seconds (p < 0·01).

ST SEGMENT CHANGES

Figure 2 shows the time to onset of 1 mm ST segment depression in those patients who developed it. On the control day 1 mm ST segment depression occurred earlier in the second exercise test in five patients and at the same stage in 11 patients. On the test day it was seen earlier in 15 patients during the second test and at the same time in five patients (p < 0·05).

HEART RATE AND BLOOD PRESSURE

Table 1 shows the mean (SEM) values of heart rate with the patients sitting, standing, and at the end of exercise. Model based estimates indicated that heart rate was eight beats per minute higher after the meal when the patients were sitting (p < 0·05) and 10 beats per minute when they were standing (p < 0·01).

There was no significant effect of the meal on systolic or diastolic blood pressure at any time. The double product (mean arterial blood pressure × heart rate) measured with the patients sitting was 6329 (381) and 6228 (457) on the control day and 6277 (323) and 6844 (530) on the test day. These values were not significantly different and the changes in double product were not related to exercise time after the meal.

CARDIAC OUTPUT

All patients were capable of performing the respiratory manoeuvres needed for cardiac output to be calculated. Table 2 shows the values of cardiac output with the patients sitting, standing, and the last measurement obtained during the exercise test. The variable number of patients who completed a measurement during exercise are also shown. Model based calculations show that the meal increased cardiac output by 0·86 l/min with the patients sitting (p < 0·01) and by 0·89 l/min (p < 0·01) with them standing. The effect of the meal, however, was not significant at or near peak exercise.

The increase in resting measurements of cardiac output in response to the meal was a useful predictor of the decrease in exercise after the meal. Adding the change in cardiac output to a regression model relating post-meal exer-

Table 1 Mean (SEM) values of heart rate (beats/minute) with the patients sitting, standing, and at the end of exercise

	Control day		*Test day*		*Change in control post − pre*	*Model based effect of meal*
	Pre	*Post*	*Pre*	*Post*		
Sitting	66·9 (2·6)	65·1 (2·4)	64·8 (2·3)	71·1 (3·4)	−0·94	8·34*
Standing	75·7 (2·7)	74·9 (2·6)	72·7 (2·5)	82·4 (3·0)	−0·78	10·43†
End point	106·9 (5·5)	107·2 (5·7)	111·6 (5·0)	109·9 (5·5)	0·19	−2·00

*p < 0·02, †p < 0·01.

Table 2 Mean (SEM) values of cardiac output with the patients sitting, standing, and the last value obtained from those in whom measurements were made during exercise

	Control day		*Test day*		*Change in control post − pre*	*Model based effect of meal*
	Pre	*Post*	*Pre*	*Post*		
Sitting	4·0 (0·2)	3·9 (0·2)	4·0 (0·2)	4·8 (0·2)	−0·02	0·86*
Standing	3·8 (2·7)	3·9 (2·6)	3·9 (2·5)	4·8 (3·0)	0·03	0·89*
End point	8·3 (0·5)	7·9 (0·5)	8·4 (0·5)	8·8 (0·4)	−0·44	1·01
Number at end point	18	21	16	20		

*p < 0·01.

cise time to pre-meal time significantly improved the predictive accuracy ($p = 0{\cdot}039$).

Discussion

In this study we showed that the exercise tolerance of patients with angina can be reduced quite substantially by a modest meal. We also showed that this reduction in exercise tolerance is related to the increase in cardiac output in response to the meal.

The fact that a meal may worsen the symptoms of some patients with angina is clinically well recognised[1, 10] but it has been surprisingly difficult to demonstrate with any consistency the mechanism. It has been known for many years that a meal increases cardiac output[11] but more recent attempts to confirm the original observation have often been unsuccessful.[2, 3] In part this is likely to be because the invasive techniques used in themselves can cause changes in haemodynamic function and thereby mask the expected post-prandial increase in cardiac output. Non-invasive techniques have proved more reliable in showing the changes in cardiac output after food.[12] In normal volunteers we showed that a modest meal may increase resting cardiac output by up to 30%.[7] The present study showed a similar increase in cardiac output at rest which was maintained and was additive to the changes during submaximal exercise. Furthermore, there was a relation between the changes in cardiac output and the change in exercise tolerance of the patients such that those patients who had the greatest increase in cardiac output had the greatest reduction in exercise tolerance.

In the absence of demonstrable changes in cardiac output the post-prandial worsening of angina has previously been ascribed to an increased myocardial oxygen consumption shown by an increase in the product of heart rate and blood pressure.[4] Although there is evidence that patients develop angina within a fairly narrow range of double product for each individual[4] the effect of food may be paradoxically to lower the double product by a reduction in blood pressure. In our study we saw the expected increase in heart rate but little change in either systolic or diastolic blood pressure and little change in the double product. The factors that determine myocardial oxygen consumption are complex and the combination of blood pressure and heart rate can only be an approximation.[13, 14] The pumping action of the myocardium is of obvious importance because this must relate directly to energy consumption and therefore oxygen utilisation; but until now, reliable non-invasive measurements of cardiac output have not been possible. It is therefore not surprising that the increase in cardiac output we showed in this study is more closely related to the reduction in patients' symptom limited exercise tolerance than changes in double product.

The factors responsible for the increase in cardiac output are unclear. Digestion is a metabolically active process that is associated with an increase in systemic oxygen consumption. Gut blood flow is increased[15] and this seems to be met by an increase in cardiac output. Redirection of blood from other vascular beds does not contribute to the enhanced blood supply to the gut. Part of the physiological stimulus for the increased cardiac output is increased activity of the sympathetic nervous system and this has implications for the treatment of post-prandial angina.[16] Drugs, such as β blockers, may prevent the increase in cardiac output with obvious benefit. An alternative way of treating patients would be with agents that prevent the increase in gut blood flow or alternatively redirect blood from other tissues and obviate the need for an increase in cardiac output. Patients may find that taking smaller meals more frequently is helpful.

A meal is an important cause of worsening of patients' angina. Its effects are related to the magnitude of the increase in cardiac output and treatment will depend upon the prevention of this increase.

1 Heberden W. Some account of a disorder of the breast *Medical Transactions of the College of Physicians of London* 1772;2 59–67.

2 Goldstein RE, Redwood DR, Rosing DR, Beiser GD, Epstein SE. Alterations in the circulatory response to exercise following a meal and their relationship to post-prandial angina pectoris. *Circulation* 1971,44·90–100.

3 Jones WB, Thomas HD, Reeves TJ. Circulatory and ventilatory responses to postprandial exercise. *Am Heart J* 1965;69 668–76

4 Robinson BF Relation of heart rate and systolic blood pressure to the onset of pain in angina pectoris. *Circulation* 1967,35·1073–83.

5 Potter JF, Heseltine D, Hartley G, Matthews J, Macdonald IA, James OFW Effects of meal composition on the postprandial blood pressure, catecholamine and insulin changes in the elderly. *Clin Sci* 1989;77.265–72.

6 Cowley AJ, Stainer K, Murphy DT, Murphy J, Hampton JR. A non invasive method for measuring cardiac output: the effect of Christmas lunch *Lancet* 1986,ii·1422–3.

7 Yi JJ, Fullwood L, Stainer K, Cowley AJ, Hampton JR. Effects of food on the central and peripheral haemodynamic response to upright exercise in normal volunteers *Br Heart J* 1990;63:22–5

8 Armitage P, Berry G. *Statistical methods in medical research.* 2nd ed Oxford Blackwell Scientific Publications, 1987.

9 Payne CD, ed. *The GLIM system release 3.77, revision a.* Oxford Numerical Alograthims Group, 1986.

10 Wayne EJ, Graybiel A Observations on the effect of food, gastric distension, external temperature and repeated exercise on angina of effort, with a note on angina sine dolore. *Clin Sci* 1934;1 287–304

11 Grollman A Physiological variations in the cardiac output of man. *Am J Physiol* 1929,89.366–70.

12 Kelbæk H, Munck O, Christensen NJ, Godtfredsen J. Central haemodynamic changes after a meal. *Br Heart J* 1989,61 506–9.

13 Sarnoff SJ, Braunwald E, Welch GH, Case RB, Stainsby WN, Macruz R. Hemodynamic determinants of oxygen consumption of the heart with special reference to the tension-time index. *Am J Physiol* 1958,192:148–56.

14 Braunwald E, Sarnoff SJ, Case RB, Stainsby WN, Welch GH. Hemodynamic determinants of coronary flow: effect of changes in aortic pressure and cardiac output on the relationship between myocardial oxygen consumption and coronary flow *Am J Physiol* 1958;192·157–63.

15 Qamar MI, Read AE, Skidmore R, Evans JM, Wells PNT. Transcutaneous doppler ultrasound measurement of superior mesenteric artery blood flow in man *Gut* 1986; 27·100–5.

16 Kelbaek H, Munck O, Christensen NJ, Godtfredsen J. Autonomic nervous control of postprandial hemodynamic changes at rest and upright exercise *J Appl Physiol* 1987,63:1862–5.

Avoidance of tolerance and lack of rebound with intermittent dose titrated transdermal glyceryl trinitrate

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Abstract

***Objectives*—To investigate the efficacy of transdermal glyceryl trinitrate given continuously and with a nocturnal nitrate free period.**

***Design*—Double blind placebo controlled study with two parallel limbs.**

***Setting*—Multicentre trial.**

***Patients*—52 patients randomised to receive either continuous treatment (23 patients) or intermittent treatment with an individually titrated dose (29 patients) for 14 days: both treatments were compared with placebo in a crossover fashion.**

***Intervention*—Continuous treatment with 10 mg per 24 hours of transdermal glyceryl trinitrate or intermittent transdermal glyceryl trinitrate titrated to give an arbitrary 10 mm Hg drop in systolic blood pressure (mean dose 18·2 mg) given over approximately 16 hours.**

***Main outcome measure*—Treadmill exercise stress testing and ambulatory monitoring of the ST segment after 14 days' treatment.**

***Results*—After 14 days' intermittent treatment resting supine and standing systolic blood pressure fell by 7·5 mm Hg (95% confidence interval 2·7 to 12·2) and 9·0 mm Hg (95% CI 3·4 to 14·5) respectively ($p < 0{\cdot}01$); resting heart rate was unchanged. Mean heart rate at 1 mm ST segment depression rose by 11·9 beats/min (CI 1·1 to 23·7) ($p < 0{\cdot}05$), mean time to onset of angina increased by 59 seconds (CI 10·8 to 108) ($p < 0{\cdot}05$), and total exercise duration increased by 40 seconds ($p < 0{\cdot}05$). These changes were not seen after continuous treatment. The frequency of ischaemic episodes was not reduced with either regimen nor was the circadian distribution of these episodes altered, in particular nocturnal episodes did not increase during intermittent treatment.**

***Conclusion*—Tolerance to glyceryl trinitrate was avoided by the use of individually titrated doses administered with a nocturnal nitrate free period. There was no evidence of "rebound" on ambulatory monitoring during this treatment.**

Organic nitrates have been used to treat angina pectoris for over a century[1] but their short duration of action and rapid hepatic metabolism have limited their prophylactic use. Molecular manipulations and formulation developments have considerably extended the duration of action of these drugs and led to their more widespread use. Transdermal nitrate patches maintain constant plasma concentrations of glyceryl trinitrate over 24 hours but there is controversy about tolerance and whether it detracts from the role of nitrates in the prophylactic treatment of angina.[2–4] The antianginal benefits of glyceryl trinitrate in the first few hours after the application of a patch are well recognised[5] but several studies have found either a partial[6] or complete loss of efficacy 24 hours after application of a patch.[7 8] A nitrate free interval avoided the development of tolerance during long term treatment with isosorbide dinitrate,[9] isosorbide mononitrate, and also with transdermal patches.[10]

The mechanisms of nitrate tolerance are not understood. It is thought that nitrate action is brought about by a cascade of events that affect the oxidation of important sulphydryl groups.[11] These are necessary for the production of intermediary derivatives of S-nitrosothiol, which are required to produce cyclic guanosine monophosphate, the mediator for vascular smooth muscle relaxation.[12 13] Continued administration of nitrates induces tolerance by reducing the intracellular concentration of reduced sulphydryl groups to a critical concentration.

We compared the effects of the continuous 24 hour administration of glyceryl trinitrate with that of a titrated dose and a nocturnal nitrate free interval.

Patients and methods

Ninety seven patients (79 men and 18 women) aged 34–72 years (mean 56·6 years) attending cardiology outpatient clinics at seven participating centres throughout England, Scotland, and Wales were selected for screening according to the following criteria. All had a history of chronic stable angina pectoris on effort caused by ischaemic heart disease for a minimum of three months before their selection and a positive exercise stress test (with electrocardiographic changes). All patients were ambulant, able to maintain accurate diaries of anginal attacks, and were capable of being managed for the duration of the study without the use of β blocking agents, calcium antagonists, or long acting oral nitrates. Patients were specifically excluded from study if they had had a documented myocardial infarction in the preceding three months; electrocardiographic abnormalities that might have interfered with the interpretation of the ST segment; a diastolic blood pressure >100 mm Hg; or significant renal, hepatic, haematological, or other clinically relevant concurrent conditions.

All eligible patients entered a one week, open run-in period and were maintained on sublingual glyceryl trinitrate alone. They performed a symptom limited treadmill exercise stress test according to a modified Bruce protocol. To be included in the treatment phases of the study patients had to show a positive response to sublingual glyceryl trinitrate during a second exercise stress test performed at least one hour and up to three hours later, 10 minutes after the patient had taken one (500 μg) sublingual tablet of glyceryl trinitrate. The response was defined as positive if the exercise time needed to cause 1 mm ST segment depression was $\geqslant 2$ minutes longer than during the first exercise test. During the second test, the workload was not increased beyond that required to produce 1 mm of ST segment depression in the first test; this avoided the false negative results caused by a higher workload.

The 85 patients who responded to sublingual glyceryl trinitrate were randomised to receive either a placebo controlled continuous or a placebo controlled intermittent treatment regimen lasting one month. After randomisation to the treatment regimens patients were re-randomised to active treatment followed by placebo treatment or vice versa in a balanced crossover design (2 × 2 weeks). During continuous treatment patients were treated with transdermal patches delivering 10 mg glyceryl trinitrate over 24 hours (Ciba) or a matching placebo. We selected this regimen because this was the maximum recommended dose approved by the regulatory authorities. The regimen of intermittent treatment used a dose that was titrated to achieve a 10 mm Hg fall in systolic blood pressure. Blood pressure was recorded two hours after the application of a patch. If a 10 mm Hg fall was not seen, another 10 mg/24 h patch was applied and observation repeated to a maximum of four patches (40 mg/24 h). Patients were maintained at their titrated dose for the duration of the study.

EXERCISE STRESS TEST

Patients exercised on a treadmill according to a modified Bruce protocol in the morning, three to five hours after a patch was applied. The patient was tested at the same time of day at the end of each two week treatment period. ST segment depression was measured 80 ms after the J point in the precordial lead that had first shown 1 mm ST segment depression during the first test. Significant ST segment depression was defined as planar or downsloping ST segment depression of $\geqslant 1$ mm measured 0·08 s after the J point. The following indices were recorded: time to 1 mm ST segment depression, heart rate at 1 mm ST segment depression, maximum ST segment depression, time to onset of angina, and total exercise time. All the electrocardiograms were examined and reported in a blind manner by one analyst.

HOLTER MONITORING

Holter monitoring was performed at the end of each treatment period. All patients underwent 48 hours of ambulatory ST segment monitoring with pre-gelled electrodes to record two bipolar leads: one an anterior lead CM5 and the other an inferior lead. The sites and method of application of these electrodes have been described elsewhere.[14] Two-channel recordings were then obtained on magnetic tape by a frequency modulated dual channel recorder (Oxford Medilog 2, frequency response 0·05–40 Hz). The frequency response of this system is sufficient to record and display the ST segment accurately. The tapes were then visually analysed at 60 times normal speed by an Oxford Medilog MA20 scanner; all printouts were recorded at 25 mm/s. Significant ST segment depression was defined as planar or downsloping ST segment shift of $\geqslant 1$ mm measured 0·08 s after the J point that persisted for >30 s. Significant ST segment elevation was defined as an upward shift of the ST segment of $\geqslant 1$ mm at the J point compared with the resting recording. Changes in the T wave vector were not regarded as evidence of myocardial ischaemia unless they were accompanied by significant ST segment changes.

DIARY CARD

Diary cards were supplied to record angina episodes during a two week period. The weekly attack rate was calculated by summing the daily events occurring over two weeks and standardised to obtain a mean weekly figure. Glyceryl trinitrate tablet consumption was recorded and analysed in a similar fashion.

STATISTICAL ANALYSIS

Statistical analysis was based on the mean (or median) values calculated at each time point of the study: initial visit, end of run-in, end of period 1, and end of period 2. The haemodynamic indices of the two treatment sequence groups were compared at baseline (end of run-in) by Student's t test. The effects of active and placebo treatment during the study were compared by the method of crossover analysis. Koch's non-parametric crossover method was used to compare the two treatment effects on the variables in the exercise stress test and on the angina diary cards.

Ambulatory monitoring results are expressed as a mean and standard deviation per 24 hours. Discrete data were analysed by the

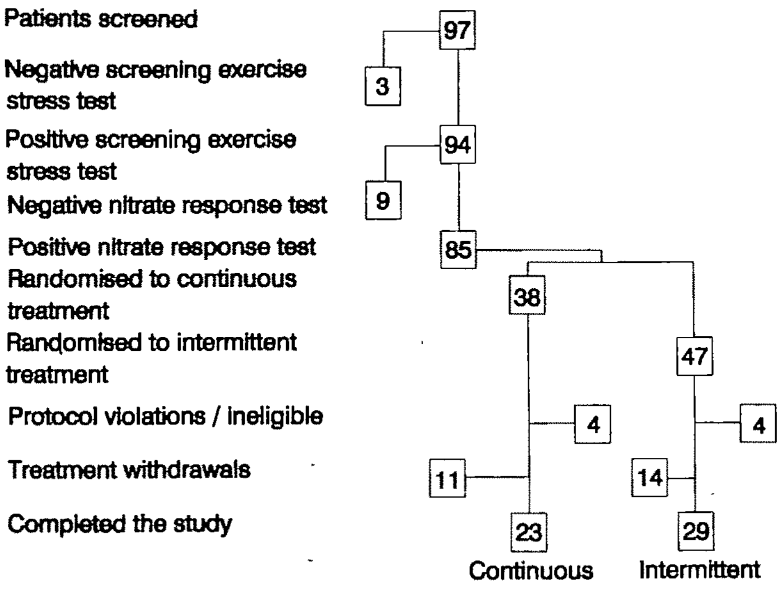
Patients screened
Negative screening exercise stress test
Positive screening exercise stress test
Negative nitrate response test
Positive nitrate response test
Randomised to continuous treatment
Randomised to intermittent treatment
Protocol violations / ineligible
Treatment withdrawals
Completed the study
97
3
94
9
85
38
47
4
4
11
14
23
29
Continuous
Intermittent

Figure 1 Flow chart to show the selection of patients to the study.

Wilcoxon signed rank test for paired observations during the double blind phase of the study. Fourier analysis was used on the hourly frequencies and durations of total ischaemia. The residual squares error was used to determine the optimum number of fitted harmonics, which was found to be a two harmonic fit, and the correlation coefficient of the fitted curve. The day was divided into four six-hour periods (01.30–07.30, 07.30–13.30, 13.30–19.30, and 19.30–01.30), and a χ^2 test with Yates's correction for continuity was applied to determine whether there was a significant excess of episodes in the morning (07.30–13.30) compared with the mean of the other three periods.

Ethical approval was obtained from each of the hospital medical committees.

Results

Ninety seven patients were screened. There were 85 nitrate responders: 38 were allocated to continuous treatment and 47 to intermittent treatment (fig 1). Twenty three patients completed the continuous treatment study and 29 patients completed the intermittent treatment study. For the intermittent treatment the mean individually titrated dose needed to cause a 10 mm Hg drop in resting systolic blood pressure was 18 mg given over 12 h; 11 patients required one patch, 14 patients two patches, two patients three patches, and two patients four patches. The demographic indices of the treatment groups were well matched.

HAEMODYNAMIC EFFECTS

After two weeks of continuous 24 h treatment with one 10 mg/h patch applied daily no clinically or statistically significant differences were found compared with placebo treatment for the following variables: heart rate and systolic and diastolic blood pressures when supine and standing. Similarly no significant differences were seen in the mean resting heart rate or supine and standing diastolic blood pressures compared with placebo treatment after two weeks' active treatment with individually titrated doses of transdermal glyceryl trinitrate. With intermittent treatment, however, the resting systolic standing and supine blood pressures were significantly reduced ($p < 0.01$) (table 1).

EXERCISE TESTING

No significant differences in favour of transdermal glyceryl trinitrate were found after continuous application compared with placebo for any of the measured exercise test end points. In contrast, intermittent treatment significantly increased the mean total exercise by 36 seconds ($p < 0.05$), the mean time to the onset of angina by 46 seconds ($p < 0.05$), and the heart rate at 1 mm of ST segment depression was increased by 9 beats/min ($p < 0.05$). In addition, time to 1 mm ST segment depression increased by 49 seconds and maximum ST segment depression was reduced by 0·11 mm; though these findings show a positive trend, they were not statistically significant (table 2).

HOLTER MONITORING

Treatment with continuous and transdermal glyceryl trinitrate did not affect the frequency of either the silent episodes of ST segment depression per 24 h or the total number of episodes of ST segment depression per 24 h. Similarly, neither the duration nor the severity of ST segment changes was affected by either treatment.

Figures 2 and 3 show the circadian distribution of the episodes of total ischaemia recorded during the placebo phase and during the two treatments. A similar circadian pattern was seen during the two treatment periods and the placebo period, with a primary peak in the morning hours and a smaller secondary peak in the evening; very few episodes were recorded during the night before 07.00 during any of the treatment periods.

Table 1 Haemodynamic results (mean) of continuous and intermittent dosing with glyceryl trinitrate

	Continuous dosing			Intermittent dosing			
Variable	*Active*	*Placebo*	*p Value*	*Active*	*Placebo*	*p Value*	*Confidence interval*
Heart rate (beats/min)	74 5	75·1	NS	76 0	78 0	NS	
Supine systolic BP (mm Hg)	142 6	133 8	NS	130 8	137 4	<0 01	2 7–12·2
Supine diastolic BP (mm Hg)	86 3	86 3	NS	83 3	86 2	NS	
Standing systolic BP (mm Hg)	138 8	135 4	NS	126 8	135 8	<0 01	3 4–14 5
Standing diastolic BP (mm Hg)	86·7	86 8	NS	84·0	85 1	NS	

BP, blood pressure. NS, not statistically significant at p < 0 05 level.

Table 2 Results (mean) of exercise testing during continuous dosing and intermittent dosing with glyceryl trinitrate

Variable	*Continuous dosing*			*Intermittent dosing*		
	Active	*Placebo*	*p Value*	*Active*	*Placebo*	*p Value*
Maximum exercise duration (min)	10·9	11·5	NS	11·3	10·7	<0·05
Time to 1 mm ST depression (min)	8·3	9·3	NS	8·7	7·9	NS
HR at 1 mm ST depression (beats/min)	115·4	119·0	NS	120·5	111·9	<0·05
Maximum ST depression (min)	1·8	1·6	NS	1·3	1·4	NS
Onset of angina (min)	7·4	8·8	NS	9·4	8·6	<0·05

NS, not statistically significant at $p < 0.05$ level.

ANGINA ATTACK RATES

The incidence of angina during treatment with placebo was low (6·6 attacks/week). Neither active treatment significantly changed this rate. The consumption of glyceryl trinitrate tablets was similarly unaltered. The incidence of nocturnal episodes was similar in all active and placebo treatment phases.

WITHDRAWALS FROM TREATMENT

Of the 85 patients who were randomised to treatment, 25 patients were withdrawn from the study, 11 receiving continuous treatment and 14 receiving intermittent treatment. A total of 17 (20%) patients were withdrawn because of headache (14 active, three placebo), and four patients (4·7%) withdrew because of local rashes (three active, one placebo). In two patients angina became worse on active intermittent treatment. One patient collapsed suddenly and died during the day while receiving active intermittent treatment. In addition, one patient on continuous treatment had so much difficulty with shift work patterns that he withdrew from the study.

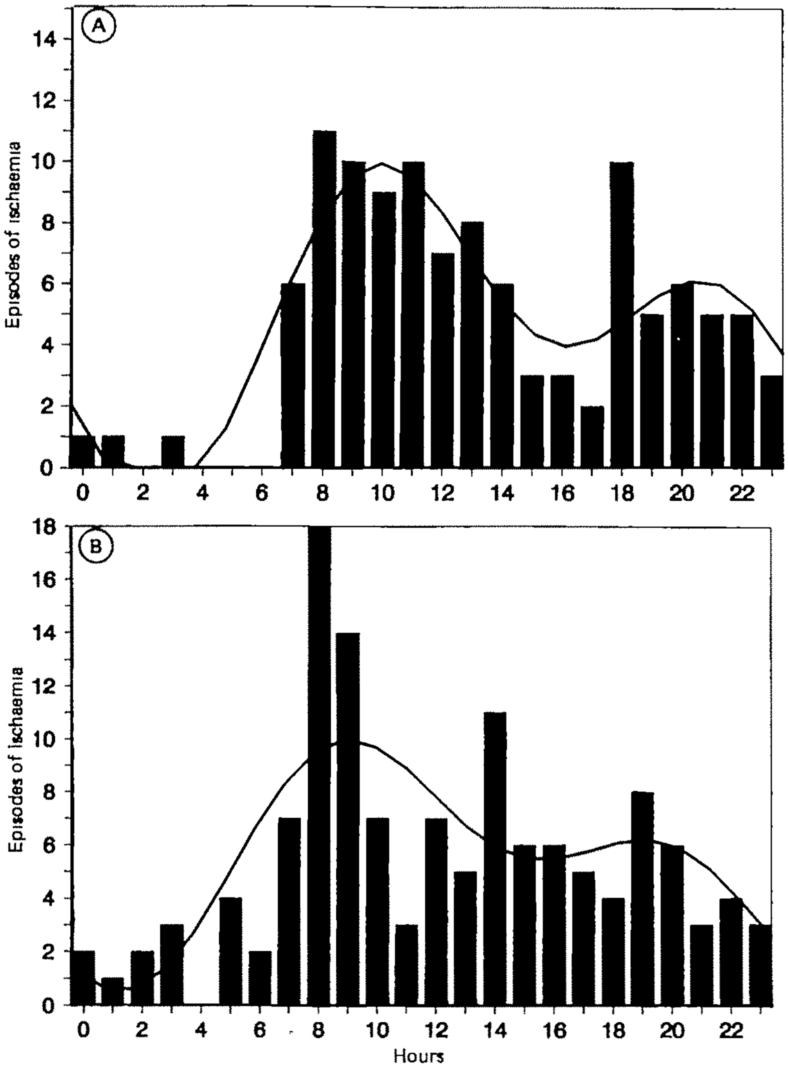

Figure 2 Twenty four hour circadian distribution of ischaemic episodes during placebo (A) and continuous transdermal nitrate treatment (B).

Discussion

The results of this study support the conclusion that transdermal glyceryl trinitrate significantly increases the total duration of treadmill exercise, the time to onset of angina, and the heart rate at 1 mm ST segment depression when these variables were measured 3–5 hours after dosing and after two weeks' treatment when individually titrated doses were used intermittently. A significantly lower systolic blood pressure beneficially affected the rate-pressure product. In contrast, the continuous treatment regimen of 10 mg/24 h was ineffective. It is not possible to conclude whether the higher doses used in the intermittent treatment group, the dosing interval, or a combination of the two helped to avoid the development of tolerance.

Tolerance to the hypotension and headache produced by organic nitrates has been known for over 80 years and is well accepted, but the magnitude and clinical relevance of tolerance to the anti-ischaemic and antianginal effects of organic nitrates have generated much controversy. There is evidence of a predictable improvement when organic nitrates are given three or four times a day during long term treatment,[15 16] and an anti-ischaemic effect has been claimed in patients who applied transdermal glyceryl trinitrate patches daily during chronic treatment.[17] Other studies, however, report significant tolerance after long term use of oral long acting nitrates[18 19] and transdermal patches.[20 21] Also, Moreyra and Kostis showed that a glyceryl trinitrate patch applied a few hours before coronary arteriography resulted in significant coronary artery dilatation, but when the patch was applied 24 hours beforehand this effect was strongly attenuated.[22]

This study accords with earlier studies which show that transdermal nitrates are effective when given intermittently,[8] though interestingly Waters *et al* were unable to show a similar benefit on exercise testing of using intermittent transdermal glyceryl trinitrate; in most patients the side effects outweighed any demonstrable benefit.[23] Recently in a large multicentre study of 206 patients a nitrate free

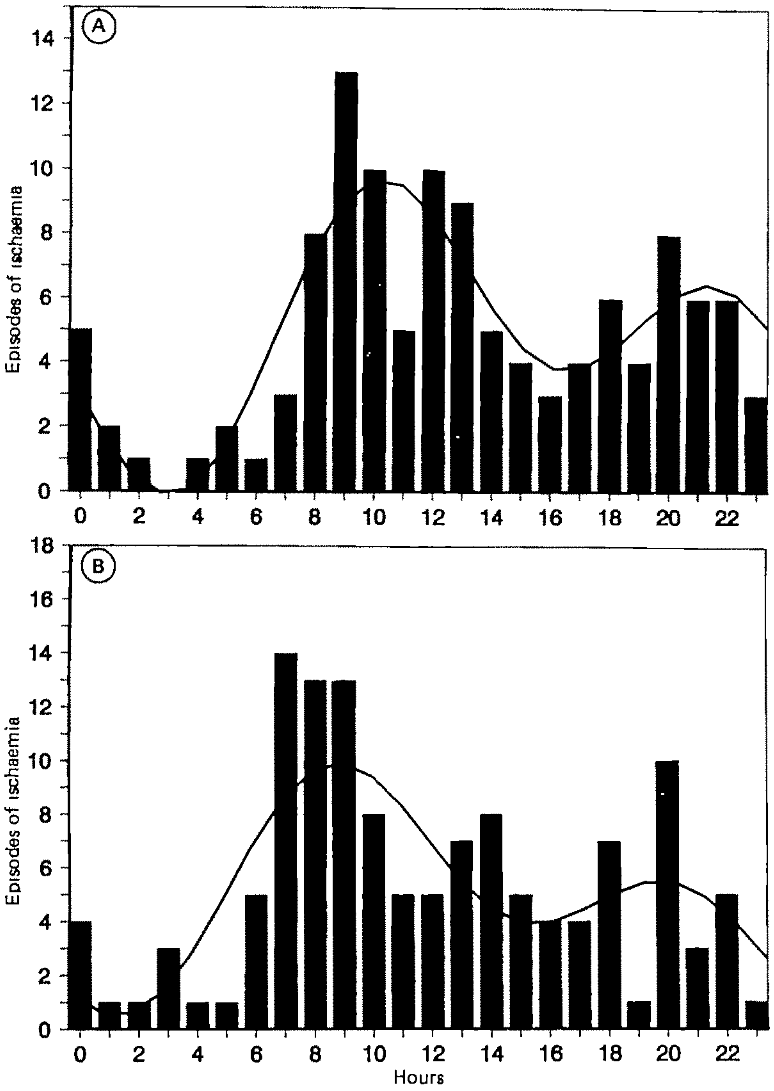

Figure 3 Twenty four hour circadian distribution of ischaemic episodes during placebo (A) and intermittent transdermal nitrate treatment (B).

period of 12 hours seemed to prevent the development of tolerance, and prolongation of exercise duration was seen during the daytime.[24] In this study, however, there were nine patients who fulfilled the defined criteria for a significant increase in rest angina during the nitrate-free periods during active intermittent treatment; in addition, the results for exercise testing before the reapplication of the patch the following morning were less good than with placebo. This has raised the question that "rebound" may be a real if rare phenomenon in patients treated with transdermal glyceryl trinitrate as monotherapy. In our study we investigated the circadian distribution of total and silent ischaemic episodes. We found that transdermal glyceryl trinitrate given intermittently or continuously did not alter the circadian distribution of ischaemic episodes and in particular that intermittent treatment was not associated with an increase in episodes during the night time hours. Clearly this does not rule out rebound in isolated cases but it does suggest that it must be rare if it occurs at all.

We thank Ciba-Geigy Pharmaceuticals for their support for the study, and in particular Dr M A Ford who helped set up and coordinate the trial

1 Brunton TL. Use of nitrite of amyl in angina pectoris *Lancet* 1867,ii 97–8

2 Charash B, Scheidt SS. The controversy over transdermal nitroglycerin: an update. *Am Heart J* 1986,112:215–7

3 Abrahams J. The brief saga of transdermal nitroglycerin discs paradise lost? *Am J Cardiol* 1984,54 220–4.

4 Zeller FP, Klamerus K. Controversies in the use of transdermal nitroglycerin systems *Clin Pharmacol* 1987,6. 605–16

5 Cerri B, Grasso F, Cefis M, *et al.* Comparative evaluation of the effect of two doses of Nitroderm TTS on exercise related parameters in patients with angina pectoris *Eur Heart J* 1984,5 710–5

6 Colombo G, Favini G, Aglieri S, *et al* Nitroderm TTS in exercise induced angina pectoris—a randomised double blind study. *Int J Clin Pharmacol* 1985,23 211–4

7 Crean PA, Ribeiro P, Crea F, *et al* Failure of transdermal nitroglycerin to improve chronic stable angina a randomized, placebo-controlled, double-blind, double cross over trial. *Am Heart J* 1984;108 1494–500

8 Cowan JC, Bourke JP, Reid DS, *et al* Prevention of tolerance to nitroglycerin patches by overnight removal *Am J Cardiol* 1987,60:271–5

9 Parker JO, Fung HL, Ruggirello D, *et al* Tolerance to isosorbide dinitrate rate of development and reversal *Circulation* 1983,68 1074–80.

10 Luke R, Sharpe N, Coxon R Transdermal nitroglycerin in angina pectoris. efficacy of intermittent application *J Am Coll Cardiol* 1987;10 642–6

11 Needleman P, Johnson EM Jr Mechanism of tolerance development to organic nitrates. *J Pharmacol Exp Ther* 1973;184 7009–15.

12 Ingarro LJ, Lippton H, Edwards JC, *et al* Mechanism of vascular smooth muscle relaxation by organic nitrates, nitrates nitroprusside and nitric oxide. evidence for the involvement of S-nitrosothiols as active intermediates. *J Pharmacol Exp Ther* 1981,218 739–49

13 Allexsson KL, Anderson RG Tolerance towards nitroglycerin, induced in vivo, is correlated to a reduced cGMP response and an alteration in cGMP turnover *Eur J Pharmacol* 1983;88·71–9.

14 Quyyumi AA, Mockus L, Wright C, Fox KM Morphology of ambulatory ST segment changes in patients with varying severity of coronary artery disease. investigation of the frequency of nocturnal ischaemia and coronary spasm. *Br Heart J* 1985;53 186–93

15 Lee G, Mason DT, DeMaria AN Effects of long term and administration of isosorbide dinitrate on the antianginal response to nitroglycerin. absence of cross-reference and self-tolerance shown by exercise testing *Am J Cardiol* 1978,41.82–7

16 Danahy DT, Aronow WS Hemodynamics and antianginal effects of high dose oral isosorbide dinitrate after chronic use *Circulation* 1977,56 205–12

17 Muieson G, Agabiti-Rosei E, Muiesan L, *et al.* A multicenter trial of transdermal nitroglycerin in exercise induced angina individual antianginal response after repeated administration *Am Heart J* 1986,112 233–8

18 Thadani U, Fung HL, Darke AC. Oral isosorbide dinitrate in angina pectoris comparison of duration of action and dose-response relation during acute and sustained therapy *Am J Cardiol* 1982,49·411–7.

19 Silber S, Krause KH, Garner C, Thiesen K, Jahrmarker H. Anti-ischemic effects of an 80 mg tablet of isosorbide dinitrate in sustained-release form before and after 2 weeks treatment with 80 mg once daily or twice daily *Z Kardiol* 1983;72(suppl 3):211–7

20 Reichek N, Priest C, Zimrin D, *et al* Antianginal effects of nitroglycerin patches *Am J Cardiol* 1984,54.1–7

21 Thadani U, Hamilton SF, Olson E, *et al* Transdermal nitroglycerin patches in angina pectoris *Ann Intern Med* 1986;105 485–92

22 Moreyra AE, Kostis JB. Effect of cutaneous nitroglycerin patches on coronary artery diameter issues concerning development of tolerance *J Am Coll Cardiol* 1989;13 428–33

23 Waters DD, Juneau M, Gossald M, Choquette G, Brien M Limited usefulness of intermittent nitroglycerin patches in stable angina *J Am Coll Cardiol* 1989,13 421–5

24 DeMots H, Glasser SP. Intermittent transdermal nitroglycerin therapy in the treatment of chronic stable angina *J Am Coll Cardiol* 1989;13 786–93

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Mitral valve repair: a valuable procedure with good long term results even when performed infrequently

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Abstract

***Objective*—To assess the results of mitral valve repair in a series with a low frequency of repair despite a policy to conserve the valve whenever possible.**

***Design*—Retrospective review of case notes with clinical and echocardiographic examination of survivors.**

***Setting*—Cardiac surgery unit in a university teaching hospital.**

***Patients*—62 consecutive patients undergoing mitral valve repair by one surgeon between 1979 and 1989.**

***Interventions*—Mitral valve repair according to the criteria and techniques of Carpentier.**

***Main outcome measures*—Frequency of repair, operative mortality, actuarial survival, freedom from reoperation and thromboembolism, clinical state, and echocardiographic state.**

***Results*—The 62 patients, median age 58 years (interquartile range 51 to 64 years), represent 14% (70% confidence interval 12% to 15%) of the 454 mitral valve operations performed in the study period. Operative mortality was 8% (70% CI 5% to 13%). Actuarial survival was 62% (70% CI 43% to 81%) at nine years. At nine years actuarial freedom from reoperation was 91% (70% CI 79% to 102%) and freedom from thromboembolism 91% (70% CI 80% to 102%). At a median follow up of 33 months (interquartile range 21 to 74 months), 38 of 46 survivors had improved functional state. Of 21 patients who underwent echocardiography one had severe mitral regurgitation and one mitral stenosis.**

***Conclusion*—Although compared with other reports of mitral valve repair the prevalence of repair was low in this series the results are comparable and justify a positive approach to repair in all patients undergoing mitral valve surgery even if this can only be achieved in a small proportion of patients.**

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In the hands of surgeons committed to the procedure mitral valve repair gives excellent results[1] but many doubt whether a policy to repair rather than replace the mitral valve is justified when only a few of the patients they see are suitable for repair. Despite the limitations imposed by a population with mitral valves which are often diseased beyond conservation, we have pursued a policy of considering repair in all patients having mitral valve surgery. This study reports the results of the first 10 years of this policy.

Patients and methods

PATIENTS AND FOLLOW UP

The study period (1 January 1979 to 26 April 1989) was the first 10 years of a policy to consider repair in all patients having mitral valve surgery. For this period all patients having mitral valve surgery, performed by one surgeon in one hospital, were identified from records of operations. For those undergoing repair information was collected by review of the hospital notes. Patients who were still alive were reviewed in the outpatient clinic and further information was obtained from a history and clinical examination. All survivors were also invited to undergo echocardiographic examination at a separate visit. Details of those patients who died outside our hospital were acquired from their local hospital or general practitioner or both. Death was considered to be valve related unless there was clear evidence of another cause.

SURGICAL TECHNIQUE

All procedures were performed through a median sternotomy while the patient was on cardiopulmonary bypass with moderate hypothermia, cold St Thomas' cardioplegia, and topical cold saline.

Mitral valve repair was carried out according to the criteria and techniques described by Carpentier.[2] A Carpentier-Edwards mitral valve annuloplasty ring was used in all repairs.

The adequacy of the repair was assessed by filling the left ventricle with saline injected through the valve and also by putting a finger in the left atrium while the heart was supporting the circulation. This was then confirmed by monitoring the left atrial pressure trace while the patient was coming off bypass and for the first 24 hours after operation.

ANTICOAGULATION

All patients were anticoagulated with warfarin for three months; this treatment was continued indefinitely if the patient had atrial fibrillation.

STATISTICAL ANALYSIS

Continuous variables are presented as median values with the interquartile range. Propor-

Table 1 Preoperative characteristics of 62 patients (median age 58, interquartile range 51–64) undergoing mitral valve repair 1979–1989

Characteristic	*No (%)*
Male:female ratio	26:36 (42:58)
NYHA class:	
I	3 (5)
II	17 (27)
III	27 (44)
IV	15 (24)
Atrial fibrillation	31 (50)
Previous cardiac operation	6 (10)
History of thromboembolism	1 (2)
Mitral stenosis	11 (18)
Mitral regurgitation	37 (60)
Stenosis and regurgitation	14 (22)

NYHA, New York Heart Association.

Table 2 Aetiology of mitral valve disease in 62 patients undergoing mitral valve repair 1979–1989

Aetiology	*No (%)*
Rheumatic	26 (42)
Degenerative	26 (42)
Post endocarditis	6 (10)
Ischaemic	4 (6)

Table 4 Repairs performed in 62 patients undergoing mitral valve repair 1979–1989

Procedure	*Number*	*% of total*
Ring and open valvotomy	20	32
Ring and quadrangular resection	13	21
Ring only	10	16
Ring and chordal shortening	7	11
Ring and repair leaflet perforation	3	5
Ring and chordal transposition	3	5
Ring and chordal fenestration	3	5
Ring, open valvotomy, and chordal fenestration	2	3
Ring and chordal resection	1	2

tions are given with 70% confidence intervals (70% CI) where appropriate. Comparisons between the first and second halves of the series for operative mortality and the proportion of patients undergoing repair were made by Fisher's exact test and the χ^2 test respectively. Actuarial survival, freedom from reoperation, and freedom from thromboembolism were calculated by the method of Kaplan and Meier and the results were given with 70% confidence intervals.

Results

PATIENTS

During the study period a total of 454 mitral valve operations were performed; of these 62 (14%, 70% CI 12% to 15%) were repairs. Table 1 shows the details of these patients. We were able to trace all patients and follow up is therefore complete at a median of 36 months (interquartile range 24 to 110 months).

NATURE OF THE VALVE DISEASE AND OPERATIONS PERFORMED

Table 2 shows the aetiology of the mitral valve disease and table 3 the nature of the valve lesions, classified by the functional approach of Carpentier[2] and by anatomical defect. Tables 4, 5, and 6 show the types of repair, the ring sizes used, and the associated cardiac procedures respectively.

Table 3 Functional and anatomical classification of valve lesions in 62 patients undergoing mitral valve repair 1979–1989

Functional classification	*Number (% of total)*	*Anatomical lesion*	*Number (% of total)*
I	13 (21)	Dilated annulus	10 (16)
		Perforated leaflet	3 (5)
II	23 (37)	Ruptured chordae	16 (26)
		Elongated chordae	7 (11)
III	26 (42)	Commissural fusion	17 (27)
		With fused chordae	9 (15)

FREQUENCY OF REPAIR

During the course of the study an increasing proportion of valves were repaired. In the first five years 8% (70% CI 6% to 10%) of valves were repaired. In the second five years from 1 January 1984 to 26 April 1989, 22% (70% CI 18% to 25%) of valves were repaired (χ^2 16·8, $p < 0{\cdot}001$).

OPERATIVE MORTALITY

Five patients died within 30 days of operation. There were no in-hospital deaths beyond 30 days, giving an operative mortality of 8% (70% CI 5% to 13%). Table 7 shows the causes of death. Three of the deaths occurred in the first two years of the series. Operative mortality for the first half of the series was 14% (70% CI 6% to 23%) and for the second 5% (70% CI 2% to 10%) (Fisher's exact test $p = 0{\cdot}24$). Those who died had a median age of 60 years.

LATE MORTALITY

There were six late deaths. Only two of these were valve related. The actuarial survival, including operative deaths, is 90% (70% CI 86% to 95%) at one year, 79% (70% CI 68% to 89%) at five years, and 62% (70% CI 43% to 81%) at nine years (fig 1).

REOPERATION

Five patients, all with rheumatic mitral valve disease, required reoperation.

One patient suddenly developed mitral regurgitation 27 days after an initially satisfactory repair. At emergency reoperation the prosthetic ring was found to be partially detached from the annulus. Four further

Table 5 Carpentier-Edwards mitral annuloplasty ring sizes used in 62 patients undergoing mitral valve repair 1979–1989

Ring size (mm)	*Number (%)*
26	2 (3)
28	11 (18)
30	22 (35)
32	19 (31)
34	6 (10)
36	2 (3)

Table 6 Associated procedures performed in 62 patients undergoing mitral valve repair 1979–1989

Associated procedures	*Number (% of total)*
Aortic valve replacement	10 (16)
Coronary artery bypass	6 (10)
Close atrial septal defect	1 (2)
Total	17 (28)

Table 7 Details of operative deaths in 62 patients undergoing mitral valve repair 1979–1989

Age (yr)	*Days post-op*	*NYHA class pre-op*	*Associated procedures*	*Cause of death*
74	24	III	CABG	Septicaemia
63	6	III		Myocardial failure
60	12	II		Haemorrhagic pancreatitis
55	1	IV		Myocardial failure
36	7	III	AVR	Ventricular fibrillation

AVR, aortic valve replacement; CABG, coronary artery bypass grafting; NYHA, New York Heart Association

patients have needed reoperation because of mitral regurgitation. In two, there was prolapse of the anterior cusp associated with elongated chordae which had not been recognised at the time of repair. Both these patients had a systolic murmur noted in the immediate postoperative period. All reoperations were needed within two years of repair.

A prosthetic valve was inserted in all patients requiring reoperation; there was no associated mortality.

The actuarial freedom from reoperation is 91% (70% CI 79% to 102%) at nine years (fig 2).

THROMBOEMBOLISM

There were six thromboembolic events in five patients. Three were major and three minor; none was lethal.

The three major thromboembolic events occurred in two patients. One developed sudden loss of consciousness and fixed dilated pupils on the second postoperative day. Consciousness was regained but the patient was left with hemiplegia. The second patient developed hemiplegia five months postoperatively. He was not taking warfarin. This drug was therefore started; but despite adequate anticoagulation he suffered a further stroke five years later.

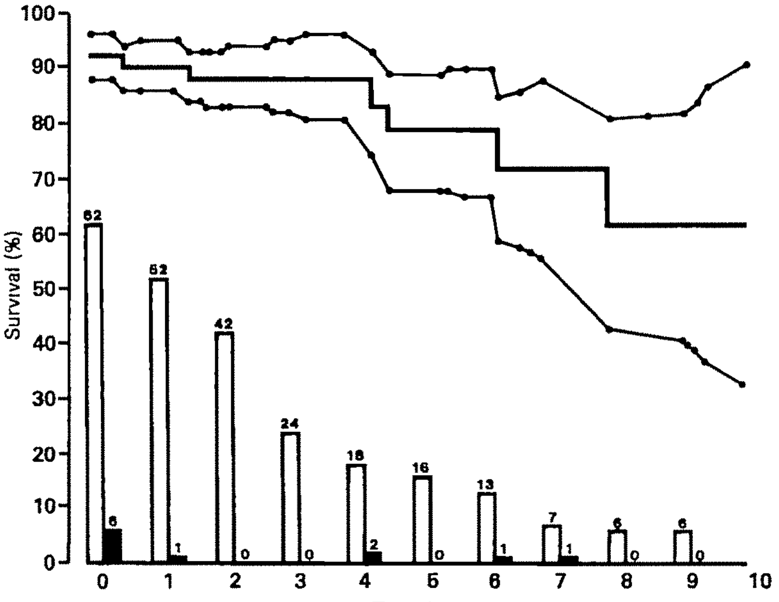

Figure 1 Actuarial survival of 62 patients undergoing mitral valve repair 1979–1989. Outer curves show 70% confidence interval, open columns show number of patients at risk at the beginning of each year, and solid columns show number of patients dying during that year

The minor events were episodes of amaurosis fugax, dysphasia, and a monoplegia. All were transient. The patient who developed dysphasia had suffered right hemiplegia after his cardiac catheterisation.

The actuarial freedom from thromboembolism at nine years was 91% (70% CI 80% to 102%) (fig 3).

ENDOCARDITIS

No patient developed endocarditis postoperatively.

CLINICAL STATE

After exclusion of those patients who have died or required reoperation 46 remain. Figure 4 shows the preoperative and postoperative functional state of these patients at a median follow up of 33 months (interquartile range 21 to 74 months).

Twenty seven patients have atrial fibrillation and all are taking warfarin. A soft systolic mitral murmur is present in 11 patients but in only one patient is this thought to represent important mitral regurgitation. This patient has a reasonable functional result at present though he may require further mitral valve surgery.

ECHOCARDIOGRAPHY

Twenty one of the 46 survivors had postoperative Doppler echocardiography; two of these were by the transoesophageal route and the remainder by conventional precordial examination. These examinations were performed at a median of 32 months (interquartile range 12 to 54 months) after operation. In eight (38%, 70% CI 26% to 49%) echocardiography showed no regurgitation, in 12 (57%, 70% CI 43% to 68%) there was mild mitral regurgitation, and one (5%, 70% CI 1% to 13%) has severe regurgitation. This is the same patient who has clinical evidence of mitral regurgitation. One patient who had an open mitral valvotomy, chordal fenestration, and insertion of a 32 mm ring, for rheumatic mitral valve disease, has evidence of mitral stenosis with a calculated valve area of 1·25 cm^2 on transoesophageal echocardiography.

Discussion

The attitude of the surgeon affects the proportion of mitral valves that are judged to be suitable for repair.[3 4] Despite a wish to repair the mitral valve whenever possible, we have managed this in only 14% of patients. This reflects the nature of the mitral valve disease that we see. Most mitral valve disease in this region is post-inflammatory; many valves are calcified with extensive fibrosis of the cusps and shortening of the subvalvar apparatus, which makes repair impossible. During the course of this study we repaired a greater proportion of valves. We attribute this rise to our increasing experience and changes in referral practice from cardiologists. Detailed comparison of these results with those of others with a higher frequency of repair is difficult because of the

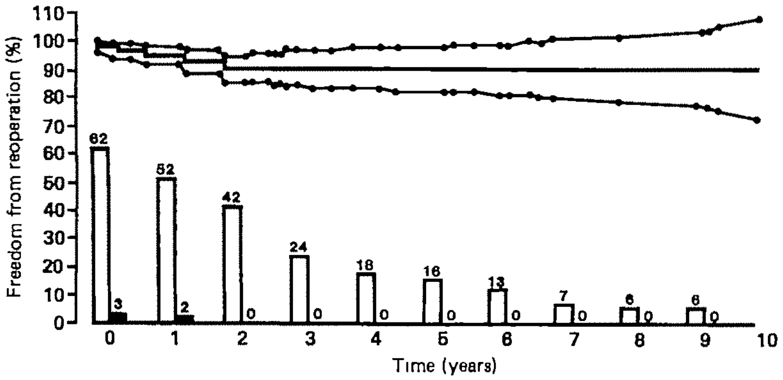

Figure 2 Actuarial freedom from reoperation of 62 patients undergoing mitral valve repair 1979–1989. Outer curves show 70% confidence interval, open columns show number of patients at risk at the beginning of each year, and solid columns show number of patients undergoing reoperation during that year.

differing patient populations reported but some broad comparisons may be made.

Our operative mortality is higher than that of recently reported series (table 8). Three of our deaths occurred during the first two years in which repair was used. Although the decrease in operative mortality to 5% in the second half of the series was not statistically significant our clinical impression is that this represents a "learning curve", an experience that has been reported by other surgeons.[10]

The variability of long term survival rates between reported series mainly reflects differing prevalences of risk factors in the patients studied.[4] This report includes "all comers" and thus represents a heterogeneous group of patients of which almost a third underwent a concomitant cardiac procedure. The long term survival, however, is similar to that of other series, some of which contain selected patients (table 8).

All reoperations became necessary within two years of repair. One was due to a technical error that caused separation of the ring. Two of the other four patients who required reoperation had early evidence of residual regurgitation and thus are examples of inadequate repair rather than failure of an initially adequate repair. The intraoperative methods used to assess the competence of repair were those in common use at the time. It is now increasingly recognised, however, that these have their limitations. The measurement of V waves in the left atrial pressure trace does not correlate with the presence or degree of mitral regurgitation assessed by left ventricular angiography[11] or by intraoperative epicardial echocardiography.[12] Filling the left ventricle with saline to test the competence of a valve repair has a false positive rate of 25% and false negative rate of 33% compared with epicardial echocardiography.[12] That these methods of assessing competence at operation are unsatisfactory is borne out by the results in this series. Two of five patients who required reoperation had residual mitral regurgitation that was not recognised at the time of operation. The use of echocardiographic techniques may improve this assessment. Epicardial and transoesophageal echocardiography were of similar sensitivity and specificity[13] and better than traditional methods.[14 15]

The cause of the mitral valve disease in all those requiring reoperation was rheumatic. Galloway *et al* found that repair was more durable in patients with degenerative disease than with rheumatic disease[9] and this accorded with Carpentier's experience.[13] Operating on patients with rheumatic valve disease Antunes *et al* found that 10·4% of their patients required reoperation within 2·6 years[5] while Cosgrove *et al* found that in a population with predominantly degenerative disease only 2·6% needed reoperation within 13·5 months.[7]

The low rates of thromboembolism, absence of endocarditis, and excellent functional results, confirmed by echocardiography, match those of the previously cited reports.

Retrospective comparisons of mitral valve

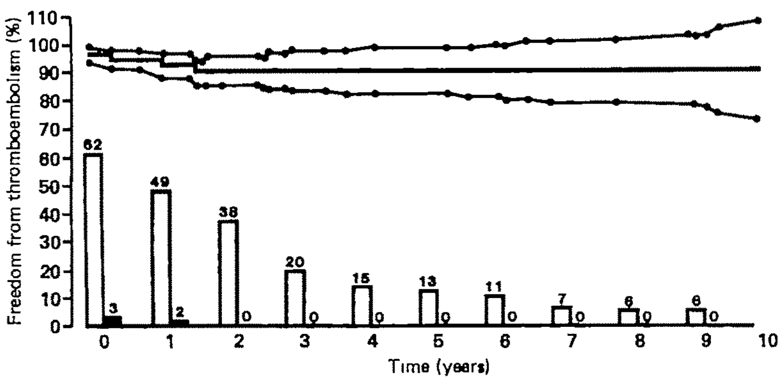

Figure 3 Actuarial freedom from thromboembolism of 62 patients undergoing mitral valve repair 1979–1989. Outer curves show 70% confidence interval, open columns show number of patients at risk at the beginning of each year, and solid columns show number of patients suffering thromboembolism during that year.

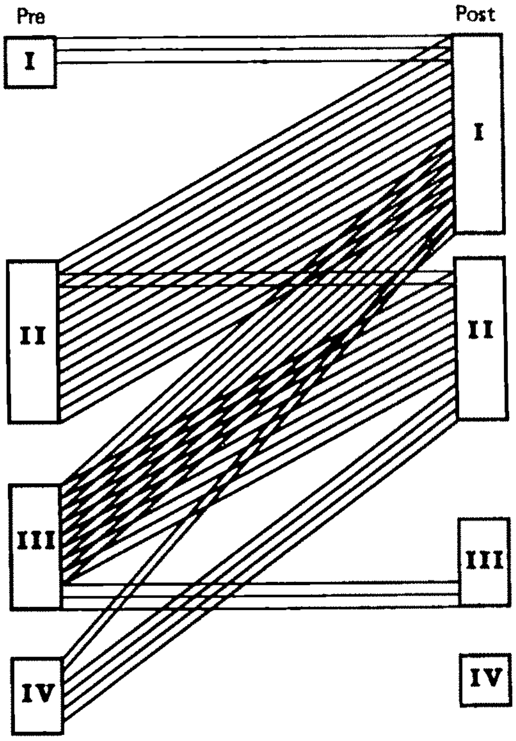

Figure 4 Preoperative and postoperative New York Heart Association class of 46 patients undergoing mitral valve repair 1979–1989 at a median follow up of 33 months.

Table 8 Recent results of mitral valve repair

Author	*Mean age of series (yr)*	*Frequency of repair (%)*	*Nature of valve disease*	*Operative mortality (%)*	*Actuarial survival (%) (yr)**	*Freedom from reoperation (%) (yr)**
Antunes *et al*[5]	22	36	Mixed, Rh	1·9	90 (4)	78 (4)
Cohn *et al*[6]	61	30	Reg, Deg	1 6	84 (4)	85 (4)
Cosgrove *et al*[7]	60		Reg, Deg	4·3	90 (2)	96 (2)
Deloche *et al*[1]	49		Reg, mixed	5·3	73 (15)	87 (15)
Eguaras *et al*[8]	45		St, Rh	1·4	98 (8)	93 (8)
Galloway *et al*[9]	51		Mixed, mixed	5 4	90 (5)	84 (5)
Sand *et al*[4]	53	21	Reg, mixed	5	76 (5)	74 (8)

Nature of valve disease: stenosed (St), regurgitant (Reg), or a combination of the two (mixed), followed by the aetiology of the valve disease (Rh = rheumatic, Deg = degenerative, mixed = various).
*Number of postoperative years at which actuarial survival and freedom from reoperation were calculated.

repair with replacement have shown significantly less valve related morbidity with repair.[4 16] In addition, preservation of the mitral valve apparatus improved postoperative left ventricular function.[17 18] This accumulating evidence of benefit and the reported safety of mitral valve repair led to the adoption of a positive approach to reparative surgery during the 10 years of this study.

With increasing experience we have repaired more valves but because we have adhered to the principle of applying reproducible techniques this has not been at the expense of satisfactory clinical results. Echocardiographic methods of intraoperative assessment should lead to further improvements. Carpentier estimated that far more mitral valves are repairable than we have found suitable,[1] even in the latter half of the series. Nevertheless, we believe that the results obtained in our patients are comparable with those of others and that repair merits consideration in all patients undergoing mitral valve surgery even if it can be achieved in only a small proportion of patients.

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1 Deloche A, Jebara VA, Relland JYM, *et al*. Valve repair with Carpentier techniques. The second decade. *J Thorac Cardiovasc Surg* 1990;99:990–1002.
2 Carpentier A. Cardiac valve surgery—the "French correction". *J Thorac Cardiovasc Surg* 1983;86·323–37.
3 Carpentier A, Chauvaud S, Fabiani JN, *et al*. Reconstructive surgery of mitral valve incompetence. Ten year appraisal. *J Thorac Cardiovasc Surg* 1980;79·338–48.
4 Sand ME, Naftel DC, Blackstone EH, Kirklin JW, Karp RB A comparison of repair and replacement for mitral valve incompetence. *J Thorac Cardiovasc Surg* 1987, 94:208–19.
5 Antunes MJ, Magalhaes MP, Colsen PR, Kinsley RH. Valvuloplasty for rheumatic mitral valve disease. A surgical challenge. *J Thorac Cardiovasc Surg* 1987;94·44–56.
6 Cohn LH, DiSesa VJ, Couper GS, Peigh PS, Kowalker W, Collins JJ Mitral valve repair for myxomatous degeneration and prolapse of the mitral valve *J Thorac Cardiovasc Surg* 1989;98·987–93.
7 Cosgrove DM, Chavez AM, Lytle BW, *et al*. Results of mitral valve reconstruction. *Circulation* 1986,74(suppl I):I-82–7.
8 Eguaras MG, Luque I, Montero A, *et al*. Conservative operation for mitral stenosis. *J Thorac Cardiovasc Surg* 1988;95:1031–7.
9 Galloway AC, Colvin SB, Baumann FG, *et al*. Long-term results of mitral valve reconstruction with Carpentier techniques in 148 patients with mitral insufficiency. *Circulation* 1988;78(suppl I):I-97–105
10 Antunes MJ, Colsen PR, Kinsley PH. Mitral valvuloplasty. a learning curve. *Circulation* 1983,68(suppl II) II-70–5
11 Fuchs RM, Heuser RR, Yin FCP, Brinker JA Limitations of pulmonary wedge V waves in diagnosing mitral regurgitation *Am J Cardiol* 1982,49 849–54.
12 Czer LSC, Maurer G, DeRobertis M, *et al*. Intra-operative evaluation of mitral regurgitation: superiority of doppler color flow mapping [abstract] *Circulation* 1986;74(suppl II):II–394.
13 Kleinman JP, Czer LSC, DeRobertis M, Chaux A, Maurer G A quantative comparison of transesophageal and epicardial color doppler echocardiography in the intraoperative assessment of mitral regurgitation. *Am J Cardiol* 1989,64:1168–72.
14 Maurer G, Czer LSC, Chaux A, *et al*. Intraoperative Doppler color flow mapping for assessment of valve repair for mitral regurgitation. *Am J Cardiol* 1987;60·333–7
15 Kyo S, Takamoto S, Matsumura M, *et al* Immediate and early postoperative evaluation of results of cardiac surgery by transesophageal two dimensional Doppler echocardiography *Circulation* 1987,76(suppl V):V-113–21
16 Galloway AC, Colvin SB, Baumann FG, *et al* A comparison of mitral valve reconstruction with mitral valve replacement: intermediate term results. *Ann Thorac Surg* 1989;47 655–62.
17 Bonchek LI, Olinger GN, Siegel R, Tresch DD, Keelan MH. Left ventricular performance after mitral reconstruction for mitral regurgitation. *J Thorac Cardiovasc Surg* 1984;88:122–7.
18 Hansen DE, Sarris GE, Niczyporuk MA, Derby GC, Cahill PD, Miller DC. Physiologic role of the mitral apparatus in left ventricular regional mechanics, contraction synergy and global systolic performance. *J Thorac Cardiovasc Surg* 1989;97:521–33

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Cardiac function after surgery for subaortic stenosis: non-invasive assessment of left ventricular performance

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Abstract

Objective—To examine left ventricular function after surgical resection of subaortic stenosis during childhood.

Design—Left ventricular performance was measured non-invasively in all patients who responded to an invitation for formal assessment.

Setting—Outpatient study, tertiary referral centre.

Patients—Twenty three (12 male and 11 female) patients (age range 3 to 31 years) of 43 consecutive patients with fixed subaortic stenosis undergoing surgical resection between 1975 and 1989 reattended for formal assessment 16 months to 15 years (median 4 years 4 months) after operation.

Main outcome measures—Left ventricular dimension, left ventricular wall thickness, left ventricular Doppler inflow velocities, and left ventricular diastolic pressure (measured from apexcardiograms). Results were compared with those in controls individually matched for age and sex.

Results—All patients were symptom free. Left ventricular cavity dimensions were normal, as was the mean fractional shortening. Posterior wall thickness tended to be greater in the patients and there was a significant increase in septal thickness. Normalised peak rate of posterior wall thinning was significantly lower in the patients and the isovolumic relaxation time was significantly shorter. Doppler inflow velocity measurements showed that early diastolic mitral flow acceleration time was normal but deceleration time was significantly shorter in the patients. The ratio of mitral flow in early diastole (E) to E plus mitral flow in late diastole (A) was significantly higher in the patients and in two patients there was complete absence of A wave flow despite large A waves on the apexcardiogram.

Conclusions—Systolic function was well preserved in patients after operation for subaortic stenosis. A restrictive pattern of left ventricular filling was common, however, and presumably reflected a response to the chronic pressure load and to surgery in the paediatric heart.

Fixed subvalvar aortic stenosis accounts for 8–10% of all left ventricular outflow tract obstructive lesions. Associated mitral and aortic valve structural abnormalities are not uncommon[1] and the incidence of aortic incompetence is also high.[2-4] Early surgical removal is usually associated with good relief of the obstruction[5 6] but asymptomatic recurrence is well described.[1 7 8] Because of the high incidence of residual morphological and functional abnormalities we examined ventricular systolic and diastolic function in patients who had had resection for subaortic stenosis.

Patients and methods

PATIENTS

We studied patients in whom there was fixed subvalvar stenosis caused by either a thin fibrous shelf or a thick fibrous ridge demonstrated by echocardiography or angiography and confirmed at operation. We excluded patients with other forms of subvalvar obstruction.

From 1975 to 1989, 43 consecutive patients (aged 8 months to 24 years (median 9 years 8 months)) underwent surgical resection of fixed subaortic stenosis. Eleven foreign patients were lost to follow up and were excluded from the study. The remaining 32 were recalled for a formal evaluation. Of the 24 patients who responded, 23 (12 male, 11 female) had data suitable for analysis. The ages at the time of assessment ranged from 3 to 31 years (median 14 years 8 months). The follow up period ranged from 16 months to 15 years 6 months (median 4 years 4 months) from the time of the second operation.

There were two patients with von-Recklinghausen disease—one with hemi-vertebrae and severe kyphoscoliosis—and one had William's syndrome. One patient had left atrial isomerism with absence of the inferior vena cava and a left superior vena cava draining into the coronary sinus. Other cardiovascular abnormalities were found in 11 patients. A ventricular septal defect was present in six (small and restrictive perimembranous (four), subaortic (one), large and doubly committed subarterial (one). There were four patients with coarctation; three had had repair to the aorta in infancy before the subsequent operation for resection of subaortic stenosis. Cross sectional echocardiography showed an abnormal aortic valve in seven patients; three with bicuspid valves and four with three thickened leaflets. Significant right ventricular outflow tract obstruction caused by muscle bundles in the right ventricle was found in two patients. Preoperative cardiac catheterisation was performed in 21 patients. The left ventricular-aortic peak to peak gradient ranged from 20 to 105 mm Hg (56 (29) mm Hg). Aortography showed trivial aortic regurgitation in two.

The subaortic ridge was excised in all patients. Six required additional myectomy of the adjacent interventricular septum.

All six patients with ventricular septal defects had the lesions closed, five at the same operation and one eight years before the operation for subaortic stenosis. Right ventricular muscle bundles were resected in two patients: one had a ligation of a ductus arteriosus and another had coarctation repair during the same operation. At the time of operation, thickening of the aortic valve leaflets was found in four but this was not severe enough to warrant valvotomy. Four patients required a second operation because of recurrence five to 14 years after the initial resection.

All patients had a full clinical examination, 12 lead electrocardiogram, and chest radiograph. Data were also obtained individually on age (in months) and sex matched healthy controls. Controls were not matched for body surface area.

Methods

CROSS SECTIONAL DOPPLER ECHOCARDIOGRAPHY AND APEXCARDIOGRAMS

Resting cross sectional, M mode, and pulsed wave Doppler echocardiography with simultaneous electrocardiography and phonocardiography was performed with a Hewlett-Packard Sonos 1000 ultrasound system. The phonocardiogram was recorded over the point on the chest at which residual murmurs were best heard, usually at the upper left sternal edge. M mode echocardiograms of mitral and aortic valve motion and of the left ventricular cavity just below the level of the free edges of the mitral valve leaflets were recorded. Mitral Doppler flow velocity was measured in the pulsed mode from apical four chamber views with the sample volume placed between the tips of valve leaflets where the maximum flow velocity in early diastole was measured. Continuous wave Doppler was used to assess the pressure gradients across the left ventricular outflow tract by the modified Bernoulli equation. Measurements were made at rest and wherever possible at submaximal exercise. All M mode and Doppler recordings were made with a Honeywell (Ecoline 22) strip chart recorder at a paper speed of 100 mm/s.

Apexcardiograms were recorded from the point of maximum impulse over the left ventricular apex by a Cambridge transducer with a time constant of four seconds.[9-11] Recordings were made with the patient in a left lateral decubitus position unless satisfactory recordings could be obtained in the supine position and they were usually recorded at the end of normal expiration.

ANALYSIS

Digitisation of left ventricular M mode echocardiograms

Only recordings in which septal and left ventricular posterior wall echoes could be clearly identified for at least three entire cardiac cycles were digitised. Echocardiograms were digitised as previously described,[12-14] by tracing echoes from both sides of the ventricular septum and from the endocardial and epicardial surfaces of the left ventricular posterior wall. From the digitised data of three averaged beats we made plots of the septal and posterior wall echoes and measured the following features: (*a*) left ventricular dimension with measurement of the rate of change of dimension as a function of time; (*b*) fractional shortening; (*c*) peak rate of dimension increase during early diastole; and (*d*) peak rate of left ventricular posterior wall thinning.

The rate of change of dimension and wall thickness were also normalised by dividing its value by the instantaneous dimension so as to adjust for physiological variations in ventricular size, wall thickness, and systolic function. The normalisation factors improve the clinical usefulness of the indices,[12 13] especially in children where age and size vary widely.

M mode and Doppler echocardiography

Peak mitral flow velocity in early diastole (E wave) and with atrial contraction (A wave) were measured and expressed as either E/A or the ratio E/E+A.[15 16] Early diastolic mitral flow acceleration and deceleration time were also measured.[17 18] The left ventricular isovolumic relaxation period was measured as the interval from the aortic closure sound (A_2 on phonocardiogram) to the opening of the mitral valve as assessed by cusp separation on the M mode echocardiogram (18 patients) and to the onset of the flow velocity signal on the Doppler traces (15 patients). All measurements were calculated from a mean of three cardiac cycles.

Apexcardiograms

Total diastolic deflection ('A') and total vertical deflection (O–E) were measured; an A/O–E ratio >33% suggested a high left ventricular filling pressure (fig 1).

DATA ANALYSIS

All data were expressed as mean (SD). The statistical significance of differences between group means was assessed by Student's *t* test. The association between various indices of diastolic function was tested by linear correlation and multiple rank correlation coefficients.

Results

At the time of re-evaluation, one patient was in New York Heart Association class II–III. The remainder were symptom free, described their quality of life as good, and took part in full normal activities. Physical examination showed

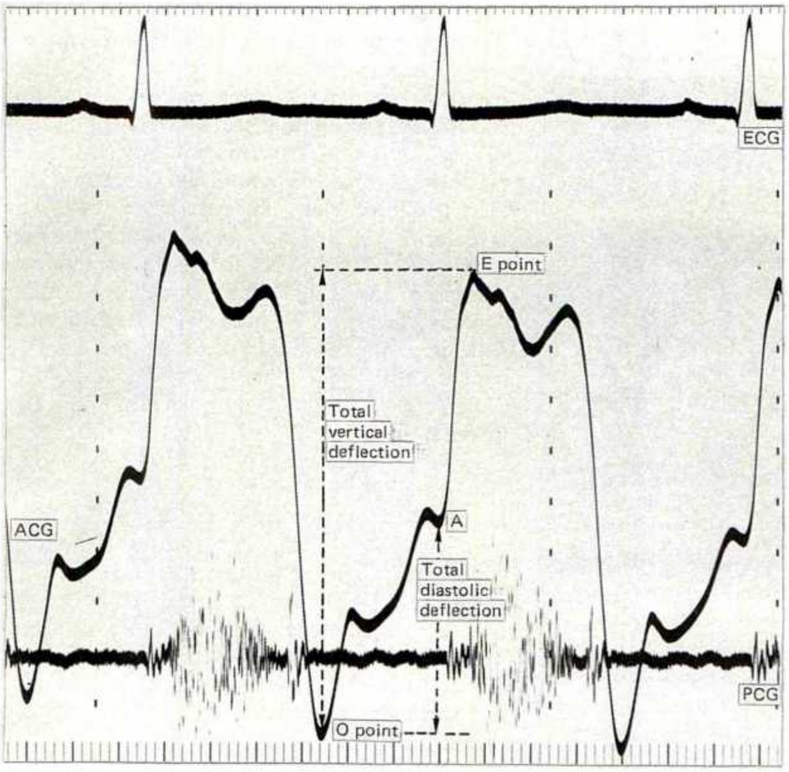


Figure 1 Apexcardiogram (ACG) from a patient with moderate restenosis. Ratio of total diastolic deflection ('A') to total vertical deflection (O-E) increased to 47%, reflecting left ventricular diastolic disease. ECG, electrocardiogram; PCG, phonocardiogram.

grade 5/6 systolic ejection murmurs at the left sternal border in two patients and grade 2–4/6 murmurs in the remainder. Fourteen patients had easily audible early diastolic murmurs. Resting electrocardiograms showed left ventricular hypertrophy in 10 patients with ST-T changes typical of strain in four. Three of these patients had residual Doppler derived gradients across the left ventricular outflow tract of 36, 52, and 85 mm Hg. There was right bundle branch block in two patients and left bundle branch block in two others. One patient had frequent unifocal ventricular extrasystoles at rest, which disappeared on exercise. There was mild cardiomegaly on the chest radiograph (cardiothoracic ratio 60%) in one patient. The heart size and pulmonary vascular markings were normal in the remaining patients.

CROSS SECTIONAL AND M MODE ECHOCARDIOGRAPHY

None of the patients with associated ventricular septal defects had residual shunts detectable with Doppler colour flow imaging. One patient with previous coarctation repair had a Doppler derived instantaneous gradient of 25 mm Hg across the repair site. Abnormal insertion of the papillary muscles of the mitral valve was noted in three patients but the peak mitral valve flow velocity was within normal limits in all. None had mitral regurgitation.

There were nine patients with evidence of mild subaortic narrowing with turbulence detectable by colour flow imaging but no definite shelf and an insignificant Doppler gradient (20 mm Hg) across the left ventricular outflow tract at rest and with exercise. Four patients had moderate to severe obstruction with recurrence of a shelf lesion in three. Continuous wave Doppler gradients across the left ventricular outflow measured from the suprasternal notch were 52, 64, and 64 mm Hg respectively, increasing to 108, 81, and 96 mm Hg with exercise in these patients. One other patient had dynamic subaortic obstruction and left ventricular concentric hypertrophy with a Doppler gradient of 85 mm Hg. The mean systolic gradient in all patients was 21 (17) mm Hg. Mild aortic regurgitation was described by Doppler echocardiography in 13 with moderate regurgitation in one other patient.

LEFT VENTRICULAR CAVITY, SEPTAL, AND POSTERIOR WALL DYNAMICS

Mean cavity dimensions at end systole and end diastole were 27·9 (0·7) mm and 43·0 (9·0) mm respectively. Neither differed significantly from those in the healthy controls (28·1 (0·4) and 42·0 (5·5) mm respectively). The mean fractional shortening was 35·3 (7·6)% in the subaortic stenosis group and 34·3 (4·9)% in the healthy controls (p = NS).

Septal thickness at end diastole was, however, significantly greater than in the healthy controls (11·8 (2·9) *v* 10·0 (2·3) mm, p < 0·05). The percentage systolic septal thickening was, however, not different (29·4 (10·4) *v* 27·5 (9·2)%, p = NS). The septal thickness correlated with the left ventricular dimension at end systole (r = 0·41, p < 0·05) and posterior wall thickness (r = 0·42, p = 0·03). In the four patients with significant residual left ventricular outflow obstruction, the septal thickness ranged from 10 to 18 mm (mean 14·8 mm).

The posterior wall thickness tended to be greater in the group with subaortic stenosis (13·9 (4·0) mm) *v* 11·9 (3·0) mm, p = 0·07). The thickness ranged from 15 to 22 mm (mean 17·8 mm) in the four patients with residual obstruction.

The normalised peak rate of posterior wall thinning was less in the study group (4·0 (1·6) s) than in the healthy controls (5·3 (1·1) s, p = 0·005). The normalised peak rate of increase of left ventricular dimension during diastole (patients 3·2 (1·1) *v* controls 3·1 + 0·8 s) was not different. There were inverse correlations between the posterior wall thinning rate and posterior wall thickness (p = 0·03) and left ventricular dimension (p = 0·03).

APEXCARDIOGRAMS

Apexcardiograms of adequate quality were recorded in 17 patients. Eight patients had a normal A/O-E ratio (< 33%). In the remaining nine the ratio ranged from 35% to 66% (mean 47%) (fig 1). The 'a' wave deflection was small in eight patients. These abnormalities were reflected in the mitral inflow Doppler recordings where both E/A and E/E+A were greater in the patients (2·14 (0·63) *v* 1·79 (0·24) and 0·73 (0·13) *v* 0·64 (0·03), respectively, both p < 0·05). Two patients with recurrence of subvalvar stenosis had absence of 'A' waves on Doppler flow studies. 'a' Waves were, however, present on the apexcardiograms and M mode echocardiograms of these patients (fig 2), sug-

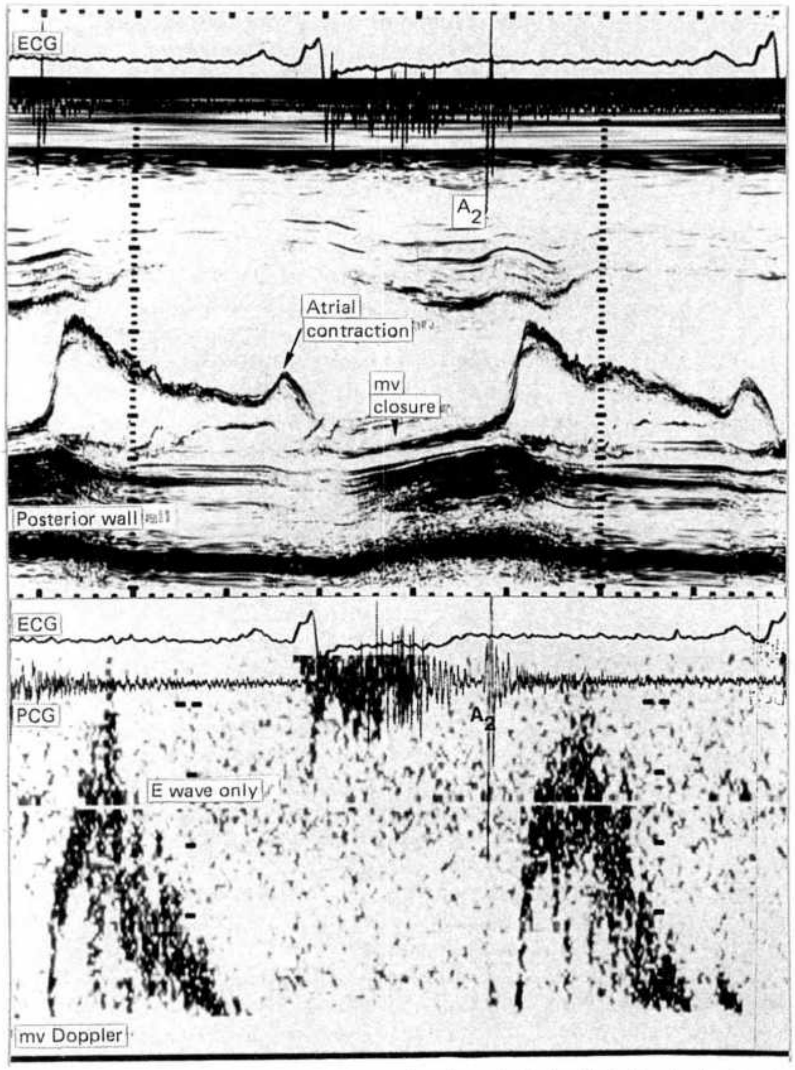


Figure 2 (Top) M mode echocardiogram taken through the level of mitral valve (mv) leaflet tips. The mitral valve opens during atrial systole. (Bottom) Transmitral flow velocity recording from the same patient showing no significant forward flow during atrial systole. ECG, electrocardiogram; PCG, phonocardiogram.

gesting the presence of mechanical atrial activity in late diastole but the inability of the left ventricle to be effectively filled during this phase of the cardiac cycle.

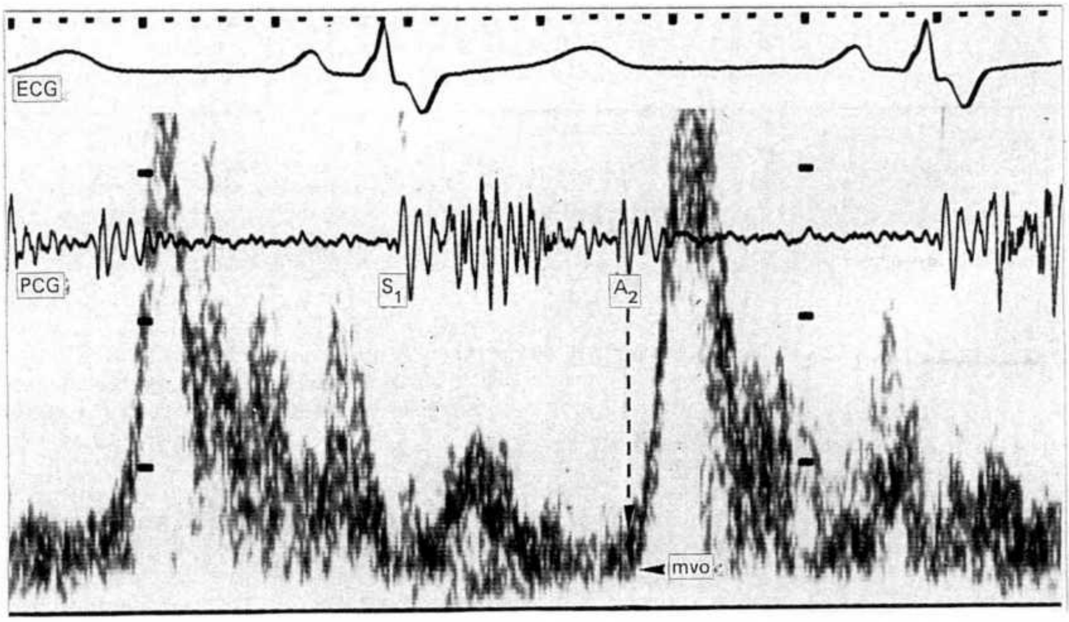
DIASTOLIC TIME INTERVALS

There was no difference in R/R interval between patients and controls (p = 0·48). Three patients had zero left ventricular isovolumic relaxation time from mitral valve Doppler flow velocity and four from mitral valve M mode recordings, two of whom had residual left ventricular outflow obstruction (fig 3). The remaining patients had an isovolumic relaxation time of 46·7 (15·0) ms from Doppler velocities and 28·2 (12·5) ms from M mode echocardiography. These were significantly shorter than those obtained in the healthy controls (59·3 (8·77) ms (p = 0·01) and 45·91 (7·81) ms (p = 0·0001) respectively). The interval between A_2 to early diastolic peak Doppler velocity (111·2 (26·9) *v* 139·6 (16·1) ms, p = 0·005) was also shorter, and the E wave deceleration time (118·6 (14·5) *v* 145·4 (25·2) ms, p = 0·005) was significantly reduced with no difference in the acceleration time (75·6 (11·8) *v* 83·1 (13·3) ms, p = NS). There were no relations between any indices measured and either age at surgery or time since surgery. Linear regression analysis (least squares) did not show any significant correlation between the degree of left ventricular hypertrophy and any of the indices of diastolic function.

Discussion

Fixed subaortic stenosis caused by a thin discrete fibrous shelf or a thick fibrous ring is present in a considerable proportion of patients with left ventricular outflow tract obstruction. Our study group is similar to others[8 19–21] in terms of preoperative severity and the 50% incidence of associated anomalies including ventricular septal defects, coarctation of the aorta, and mitral valve abnormalities. Fixed subaortic stenosis is usually progressive and most patients will require surgery. In the absence of associated severe mitral stenosis, the operative mortality or morbidity is low[1] and prolonged survival can be expected, most patients having good relief of the obstruction in the short term.[5 8 22] However, the operation may

Figure 3 Transmitral flow velocity recorded in a patient with moderate restenosis. The left ventricular isovolumic relaxation time is zero. mvo, mitral valve opening, ECG, electrocardiogram; PCG, phonocardiogram.



not be curative because of problems with residual or recurrent obstruction and aortic regurgitation in some patients.[2-4 6 8] Indeed, in our study more than half of the patients had residual left ventricular outflow obstruction of varying degrees and 14 patients had mild aortic regurgitation.

Left ventricular function was often abnormal. The septum was significantly thickened and the posterior wall showed the same tendency; mean percentage systolic thickening of the septum and posterior wall, however, were normal. The size of the left ventricular cavity at end diastole and end systole and thus fractional shortening were also normal, showing that systolic function was well preserved.

In contrast with this, diastolic left ventricular function was appreciably abnormal. The normalised peak rate of posterior wall thinning was significantly reduced as was the isovolumic relaxation time (it was 0 ms in four patients). The increase in mitral valve flow velocity in early diastole shown by Doppler inflow measurements was larger than that caused by atrial contraction in late diastole (higher E/E+A ratio). In some patients, there was complete absence of 'A' wave flow despite there being obvious 'a' waves on the apexcardiogram and M mode echocardiogram. The apexcardiograms provided further evidence of impaired diastolic function, with half of them suggesting raised end diastolic pressures. The E wave deceleration time was also significantly reduced. This type of abnormality occurs when there is a large increase in pressure per unit volume during the early diastolic filling phase,[23 24] indicating a restrictive left ventricular filling pattern.

The characteristic pattern of diastolic dysfunction we saw in our patients differs significantly from that described in adults and children with hypertrophy caused by valvar aortic stenosis,[25 26] hypertrophic cardiomyopathy, and pressure overload hypertrophy.[27 28] In all previous studies of patients with these diseases, systolic function was preserved, but isovolumic relaxation time was prolonged and wall motion incoordinate as shown by a reduced rate of dimension increase and decreased thinning rate, a lower 'E' velocity with a higher 'A' velocity and a longer deceleration time. Our results showed a quite different pattern of diastolic dynamics, which simulated a restrictive myocardial process. The isovolumic relaxation time was shorter with an increased 'E' and a small or absent 'A' and a reduced deceleration time though the thinning rate was reduced. The presence of an 'a' wave on the apexcardiogram and the absence of effective filling on Doppler flow during atrial contraction strongly suggest that end diastolic compliance is very low. The mechanisms underlying these differences are not certain.

The impact of residual problems in postsurgical subaortic stenosis may not be appreciated from a clinical examination, electrocardiogram, or resting left ventricular-aortic gradient. Most of our patients were symptom free. Our study, however, showed significant alterations in the diastolic function of the left ventricle consistent with a stiff myocardium with reduced compliance and restricted filling. Patients therefore need careful supervision, regular follow up, and postoperative haemodynamic evaluation by various means to identify those with late unsatisfactory results and to provide remedial measures as far as possible.

We thank Dr E A Shinebourne, Dr J S Carvalho, and our surgical colleagues for their assistance

1 Somerville J Fixed subaortic stenosis—a frequently misunderstood lesion. Editorial note *Int J Cardiol* 1985, 8:145–8

2 Bjorn-Hansen LS, Lund O, Nielson TT, Kromann-Hansen O, Jensen FT Aortic regurgitation after surgical relief of subvalvular membranous stenosis. a long-term follow-up study. *Scand J Thorac Cardiovasc Surg* 1988;22:275–80

3 Binet JP, Lasay J, Demontoux S, Planche C, Langlois J Subvalvular aortic stenosis long-term surgical results *Thorac Cardiovasc Surg* 1983,31 96–100.

4 Moses RD, Barnhart GR, Jones M The late prognosis after localised resection of fixed (discrete and tunnel) left ventricular outflow tract obstruction. *J Thorac Cardiovasc Surg* 1984;87·410–20.

5 Champsaur G, Trusler GA, Mustard WT Congenital discrete subvalvar aortic stenosis· surgical experience and long-term follow-up in 20 paediatric patients *Br Heart J* 1973;35·443–6.

6 Hardesty RL, Griffith BP, Mathews RA, *et al* Discrete subvalvular aortic stenosis an evaluation of operative therapy *J Thorac Cardiovasc Surg* 1977;74:352–61

7 Freedom RM, Pelech A, Brand A, *et al*. The progressive nature of subaortic stenosis in congenital heart disease *Int J Cardiol* 1985;8·137–43.

8 Somerville J, Stone S, Ross D Fate of patients with fixed subaortic stenosis after surgical removal *Br Heart J* 1980; 43:629–47.

9 Newton A, Desser KB, Benchimol A. Apexcardiogram in the assessment of left ventricular function. *Adv Cardiol* 1985,32:81–95

10 Craigie E, Damon S. Heart sounds· phonocardiography, carotid, apex and jugular venous pulse tracings, and systolic time intervals. In· Braunwald E, ed. *Heart disease—textbook of cardiovascular medicine* Philadelphia. WB Saunders, 1980 41–63.

11 Voigt GC, Friesinger GC. The use of apexcardiography in the assessment of left ventricular diastolic pressure *Circulation* 1970,41 1015–23.

12 Dawson R. Digitised M-mode echocardiograms In· St John Sutton M, Oldershaw P, eds. *Textbook of adult and paediatric echocardiography and Doppler* Boston Blackwell Scientific Publications, 1989 137–53

13 Upton MT, Gibson DG The study of left ventricular function from digitised echocardiograms. *Prog Cardiovasc Dis* 1978,20(No 5):359–84

14 Gibson DG, Brown D. Measurement of instantaneous left ventricular dimension and filling rate in man, using echocardiography. *Br Heart J* 1973,35 1141–9

15 Mirsky I. Assessment of diastolic function: suggested methods and future considerations *Circulation* 1984; 69.836–41.

16 Little WC, Downes TR Clinical evaluation of left ventricular diastolic performance. *Prog Cardiovasc Dis* 1990, 32(No 4).273–90

17 Nishimura RA, Abel MD, Hatle LK, Tajik AJ. Assessment of diastolic function of the heart· background and current applications of Doppler echocardiography. Part II Clinical studies. *Mayo Clin Proc* 1989;64 181–204.

18 Labovitz AJ, Pearson AC Evaluation of left ventricular diastolic function. clinical relevance and recent Doppler echocardiographic insights *Am Heart J* 1987;114:836–49

19 Schneeweiss A, Motro M, Shem-Tov A, Bleiden LC, Neufield HN. Discrete subaortic stenosis associated with congenital valvular aortic stenosis—a diagnostic challenge. *Am Heart J* 1982;106·55–9

20 Vogel M, Freedom RM, Brand A, Trusler GA, Williams WG, Rowe RD Ventricular septal defect and subaortic stenosis: an analysis of 41 patients *Am J Cardiol* 1983,52 1258–63.

21 Chung KJ, Fulton DR, Kriedberg MB, Payne DD, Cleveland RJ. Combined discrete subaortic stenosis and ventricular septal defect in infants and children. *Am J Cardiol* 1984;53 1429–32.

22 Edwards H, Mulder DG. Surgical management of subaortic stenosis. *Arch Surg* 1983,118:79–83

23 Appleton CP, Hatle LK, Popp RL Demonstration of restrictive ventricular physiology by Doppler echocardiography. *J Am Coll Cardiol* 1988,11.757–68

24 Appleton CP, Hatle LK, Popp RL Relation of transmitral flow velocity patterns to left ventricular diastolic function New insights from a combined hemodynamic and Doppler echocardiographic study *J Am Coll Cardiol* 1988;12·426–40

25 Fifer MA, Borow KM, Colan SD, Lorell BH Early diastolic left ventricular function in children and adults with aortic stenosis. *J Am Coll Cardiol* 1985;5.1147–54.

26 Friedman MJ, Sahn DJ, Burris HA, Allen HD, Goldberg SJ. Computerised echocardiographic analysis to detect abnormal systolic and diastolic left ventricular function in children with aortic stenosis. *Am J Cardiol* 1979;44 478–86.

27 Gibson DG, Traill TA, Hall RJC, Brown DJ. Echocardiographic features of secondary left ventricular hypertrophy. *Br Heart J* 1979;41:54–9

28 Sanderson JE, Traill TA, St John Sutton MG, Brown DJ, Gibson DG, Goodwin JF. Left ventricular relaxation and filling in hypertrophic cardiomyopathy an echocardiographic study. *Br Heart J* 1978,40·596–601

Br Heart J 1991;66:166–74

Multivariate analysis to simplify the differential diagnosis of broad complex tachycardia

Michael J Griffith, Mark A de Belder, Nicholas J Linker, David E Ward, A John Camm

Abstract

Univariate analysis has identified several criteria that aid the differential diagnosis of broad complex tachycardia. In this study of 102 consecutive patients multivariate analysis was performed to identify which of 15 clinical and 11 electrocardiographic variables were independent predictors of ventricular tachycardia. These were shown to be a history of myocardial infarction, the QRS waveforms in leads aVF and V1, and a change in axis from sinus rhythm to tachycardia of more than 40°. If none of the criteria was met, the diagnosis was almost certainly supraventricular tachycardia. If one criterion was met the diagnosis was probably supraventricular tachycardia. If two criteria were met then the diagnosis was probably ventricular tachycardia. If three or four criteria were met, the diagnosis was almost certainly ventricular tachycardia. The predictive accuracy was 93%. This was increased to 95% by including two other criteria—definite independent P wave activity and ventricular extrasystoles with the same QRS configuration as that in tachycardia. These criteria were not included in the multivariate analysis because though they were 100% specific they were seldom seen.

These four criteria can be used as simple rules in determining the origin of a broad complex tachycardia.

All previous studies on the electrocardiographic or clinical diagnosis of broad complex tachycardias have used univariate analysis to assess the value of individual diagnostic criteria.[1-8] The aim of this study was to investigate the interaction between variables and, by use of multivariate analysis, to identify the independent predictors of the diagnosis of ventricular tachycardia.

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Patients and methods

PATIENTS

Data were collected prospectively from 102 consecutive patients referred to St George's Hospital for investigation of their tachycardia between November 1986 and November 1988. Each patient had a 12 lead electrocardiogram showing broad complex uniform tachycardia (QRS width greater than 110 ms) and the definitive diagnosis was established at electrophysiological study with two to four transvenous intracardiac electrodes. The diagnosis was supraventricular tachycardia if a His potential preceded each ventricular electrogram, with a normal HV interval, or if anterograde conduction down an atrioventricular or nodoventricular accessory pathway was shown. If no His potential preceded each ventricular electrogram or the HV interval was shorter than that seen during sinus rhythm then the diagnosis was ventricular tachycardia. If a patient had tachycardia with more than one configuration, the tachycardia recorded at first presentation was analysed. Patients who had sustained a myocardial infarct in the previous seven days were excluded. The clinical data that were available on presentation were collected. These included features obtained from the history and a chest *x* ray. Secondary information that was available from the patients' records was also analysed. Electrocardiograms in both tachycardia and sinus rhythm were collected and analysed.

CLINICAL DATA

Features of the history that were assessed included:

(*a*) Age at presentation to St George's Hospital.

(*b*) A history of congestive heart failure—defined as an episode of exertional breathlessness, orthopnoea, or paroxysmal nocturnal dyspnoea (in the absence of chronic lung disease), not associated with palpitation.

(*c*) A history of angina pectoris—defined on the basis of classic symptoms when the patient was not in tachycardia.

(*d*) A history of coronary artery bypass grafting.

(*e*) A previous myocardial infarct—defined as any specific episode when the patient had been admitted to hospital with chest pain and believed that he had sustained a heart attack.

(*f*) Palpitation—defined as any history of irregular or fast heart beats.

(*g*) Syncope—defined as any episode of loss of consciousness whether or not this was related to tachycardia.

(*h*) Smoking—including current smokers and those who had given up in the year before presentation.

(*i*) A family history of ischaemic heart disease—defined as any first degree relative with angina, a previous heart attack, or who had undergone coronary artery bypass surgery.

(*j*) Chest pain during tachycardia.

(*k*) Collapse during tachycardia—defined as either loss of consciousness or a systolic blood pressure of <60 mm Hg.

In addition we noted the following results of investigation:

(*a*) The cardiothoracic ratio—calculated conventionally from the presentation posteroanterior chest radiograph taken during sinus rhythm (an abnormal ratio was defined as $>0{\cdot}55$).

(*b*) A left ventricular aneurysm—if documented on echocardiography or cardiac catheterisation.

ELECTROCARDIOGRAPHIC DATA

The electrocardiograms were recorded at a paper speed of 25 mm/s because this is the conventional speed of recording used in clinical practice. The following variables were measured:

(*a*) Width of the QRS—defined as the widest measurable QRS complex.

(*b*) RR interval during tachycardia, averaged over four beats.

(*c*) Regularity of tachycardia—defined as the maximum difference in RR interval over five consecutive beats (excluding fusion or capture beats), measured in a lead with a sharp R wave peak.

(*d*) Fusion or capture beats—defined conventionally.

(*e*) Independent P waves—these had to be approximately regular with a different rate from that of the QRS complexes.

(*f*) "Bundle branch block" pattern during tachycardia—defined on the basis of the dominant deflection in lead V1; if the QRS complex was predominantly positive, "right bundle branch block" pattern was assigned, and if it was predominantly negative it was "left bundle branch block" pattern.

(*g*) Ventricular extrasystoles—defined as wide complex beats in sinus rhythm without a preceding P wave (these extrasystoles could have been aberrantly conducted atrioventricular junctional complexes). The configuration of these beats was compared with that of the QRS complex during tachycardia in those leads in which they were recorded.

(*h*) QRS axis—measured in the frontal plane using the dominant vector in each of the six limb leads. A "normal" axis was defined as from $-30°$ to $+90°$, right axis as $+90°$ to $180°$, and left axis as $-30°$ to $-180°$.

(*i*) Change in QRS axis—defined as a difference in axis of greater than 40° between sinus rhythm and tachycardia.

(*j*) Fusion beats—defined as complexes in tachycardia that have a QRS waveform intermediate between the configuration seen during tachycardia and that expected from conduction down the atrioventricular node.

In the "left bundle branch block" tachycardias, leads V1, V2, and V6 were analysed on the basis of the criteria described by Wellens and colleagues and tested by Kindwall and coworkers.[1 2]

The configurations recorded from the leads I, aVF, V1, and V6 were based on the number, order, and relative magnitude of the Q, R, and S waves and assigned to one of 12 basic waveforms (fig 1).

ANALYSIS

Each variable was initially examined by univariate analysis for its predictive ability in the diagnosis of ventricular tachycardia. The χ^2 test was used to test differences between proportions and Student's unpaired t test was used to test for differences between continuous variables. Significance was defined at the $p < 0{\cdot}05$ level.

The configuration of the QRS complexes (1–12) in the four selected leads was analysed with respect to the final diagnosis. For each lead the number of patients with each pattern who had ventricular or supraventricular tachycardia was counted and an estimated ventricular to supraventricular tachycardia ratio (the VT/SVT ratio) was calculated. Overall in this study, 69 patients had a definitive diagnosis of ventricular tachycardia and 33 patients had supraventricular tachycardia, providing a true VT/SVT ratio of 2/1. If the estimated VT/SVT ratio of a pattern in a lead was 2/1 or greater this waveform was defined as diagnostic of ventricular tachycardia in that lead; if the ratio was less than 2/1 the waveform was defined as diagnostic of supraventricular tachycardia. This classification was necessary so that the individual lead configurations could be entered into the multivariate analysis.

It may be argued that these electrocardiographic criteria were derived from the data. Therefore a second analysis was also performed using an a priori classification of electrocardiographic configuration derived from

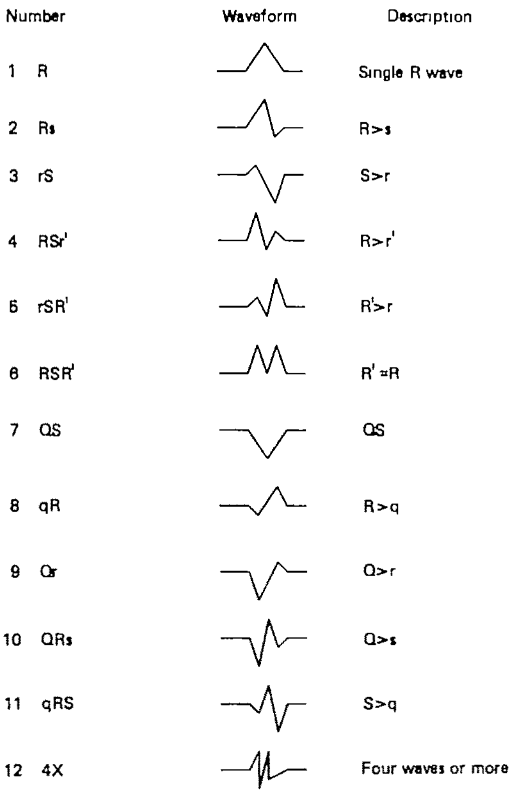


Figure 1 The 12 basic waveforms used to classify the electrocardiograms

published reports. These are only available for leads V1 and V6.[1,2,4] For V1 the diagnostic waveforms were identical to those derived from our data in patients with "right bundle branch block" tachycardia[1,4] (see figure 5) and these were combined with the criteria for ventricular tachycardia of Kindwall and colleagues[2] in patients with "left bundle branch block" pattern tachycardia. In lead V6 a Q wave or dominant S wave were classified as ventricular tachycardia (configurations 3 and 7–12) and those with a dominant R wave as supraventricular tachycardia (configurations 1, 2, 4, 5, and 6).[1,2,4] This classification had minor differences from the derived criteria for V6.

All variables that were significant by univariate analysis were then entered into multivariate analysis. However, all patients in this study who had a history of congestive heart failure, angina pectoris, or coronary artery surgery also had either a history of myocardial infarction or an abnormal cardiothoracic ratio. The latter two variables were the most powerful predictors of the diagnosis of ventricular tachycardia; the addition of the three other variables did not increase either sensitivity or specificity. Previous myocardial infarction and an abnormal cardiothoracic ratio were therefore included in the multivariate analysis in preference to the other three variables.

Independent P wave activity and ventricular extrasystoles with the same configuration as tachycardia were not included in the multivariate analysis because both were 100% specific for ventricular tachycardia and were thus diagnostic. With an iterative approach it is difficult to compare these latter two variables with other variables with less than 100% specificity. They were added to the final analysis, however, to evaluate whether they would improve the diagnostic capability. The multivariate analysis was performed with the logit model (using the LIMDEP package, version IV.2, on a personal computer[9]). This uses stepwise logistic regression to generate probabilistic functions for a binary result. This system, because it uses logistic rather than linear regression, allows the analysis of both continuous and non-continuous variables.[10,11] In the LOGIT model the probability (P) of an event occurring is expressed as the non-linear function, $1/[1 + \exp(-B.X)]$, of observable characteristics (X) and coefficients (B). The model requires a constant term, termed "constant" in the tables, which is analogous to the intercept term in least squares regression.

Results

Table 1 shows the results of univariate analysis. Many of the variables were significantly different between ventricular tachycardia and supraventricular tachycardia. Patients with ventricular tachycardia were older and were more likely to have a history of congestive heart failure, angina pectoris, coronary artery surgery, myocardial infarction, smoking, and haemodynamic collapse during the attack. They were also more likely to have an abnormal cardiothoracic ratio and a left ventricular aneurysm. The following features were electrocardiographic markers of ventricular tachycardia: the width of the QRS complex during tachycardia, the presence of independent P waves during tachycardia, ventricular extrasystoles with the same configuration as the QRS in tachycardia, left axis deviation during tachycardia, and an axis shift of greater than 40° from sinus rhythm to tachycardia. Fusion beats were seen in supraventricular tachycardia in three patients (fig 2).

Table 2 shows the incidence of the various defined waveforms in leads I, aVF, V1, and V6; and table 3 shows the estimated VT/SVT ratio for each configuration in each lead and the designated diagnosis. Certain waveforms were more predictive for each diagnosis than others.

Lead I—In "left bundle branch block" pattern tachycardia a QS or qR wave (pattern 7 or 8) was seen only in ventricular tachycardia. This lead was not helpful, however, in making the diagnosis in "right bundle branch block" pattern tachycardia.

Lead aVF—In tachycardia with a "left bundle branch block" pattern a QS or qR wave (pattern 7 or 8) was highly suggestive of ventricular tachycardia, while an Rs wave (pattern 2) was specific for supraventricular tachycardia. In "right bundle branch block" pattern tachycardia a predominantly negative

Table 1 Results of univariate analysis

Variable	*VT*	*SVT*	*p Value*
Age (yr) (mean (SD))	54.2 (16)	31.9 (15)	0 001
Sex F/M	14/55	7/26	0 91
History of			
Cardiac failure	16/69*	0/33	0 001
Angina	22/69*	1/33	0 001
Coronary surgery	9/69*	0/33	0·01
Myocardial infarct	44/69	1/33	0 001
Palpitation	49/69	28/33	0 13
Syncope	29/69	12/33	0 59
Smoking	32/69	8/33	0 05
Family history	15/69	6/32	0 95
Aneurysm	14/69†	0/33	0 001
During tachycardia:			
Chest pain	18/69	10/33	0 45
Hypotension	25/69	4/33	0 05
CTR > 0 55	33/69	1/33	0 001
	ECG variables:		
Mean (SD) QRS complex width (ms) in			
Tachycardia	156 (38)	131 (20)	0 001
Sinus rhythm	101 (22)	101 (22)	0·93
Tachycardia:			
Mean (SD)			
RR interval (ms)	356 (105)	327 (77)	0·09
Regularity (ms)	11 2 (10)	22 (59)	0·76
Fusion/capture	13/69	3/33	0 41
Independent P waves	23/69	0/33	0 001
LBBB pattern	36/69	176/33	0 94
RBBB pattern	33/69	16/33	0 94
VES with same configuration	12/69	0/33	0·001
Axis during tachycardia.			
Normal axis	5/69	14/33	
Right axis > +90°	21/69	9/33	
Left axis < −30°	43/69	10/33	0 01
Axis shift from sinus rhythm to tachycardia			
−40° to +40°	12/69	21/69	
> 40°	21/69	5/33	0 001
< −40°	36/69	7/33	

*All these patients had a history of myocardial infarction or an abnormal cardiothoracic ratio (these variables were not included in the multivariate analysis).

†Not included in the multivariate analysis as not necessarily available at presentation

CTR, cardiothoracic ratio on *x* ray; VES, ventricular extrasystole; LBBB, left bundle branch block, RBBB, right bundle branch block.

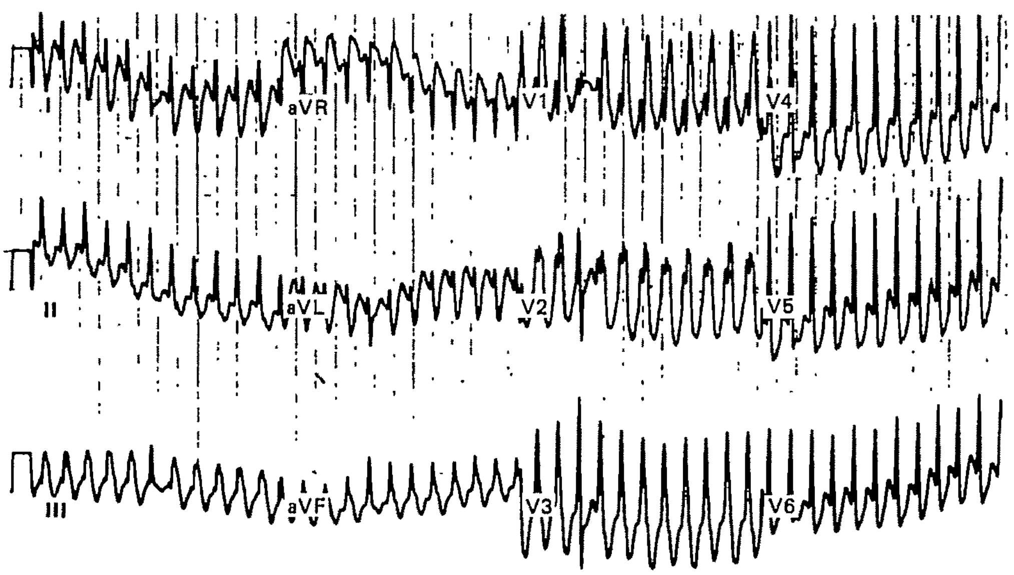


Figure 2 Supraventricular tachycardia (atrioventricular reentry tachycardia) with "fusion" beats caused by intermittent partial right bundle branch block interrupting complete right bundle branch block.

deflection was suggestive of ventricular tachycardia, especially when a Q wave was present (patterns 7, 9, and 10). Figures 3 and 4 show the predictive waveforms.

Lead VI—In "left bundle branch block" pattern tachycardia the waveform alone was not helpful in making a diagnosis. In "right bundle branch block" pattern tachycardia, a monophasic or biphasic waveform suggested ventricular tachycardia (patterns 1, 2, or 8); a triphasic RsR′ or rSR′ configuration suggested supraventricular tachycardia (pattern 5 or 6), unless the amplitude of the R wave was greater than that of the R′ wave (pattern 4). Figure 5 shows the predictive waveforms.

Lead V6—Overall this lead was not helpful in making the diagnosis in "left bundle branch block" pattern tachycardia, although a Q wave was specific for ventricular tachycardia (patterns 7–11). In "right bundle branch block" pattern tachycardia a Q wave (pattern 7 or 8) or an RS wave with S > R (pattern 3) was suggestive of ventricular tachycardia. Table 4 shows the predictive accuracy of each lead when the above criteria were used. Lead aVF had the highest predictive accuracy (73%); the other three leads each had a predictive accuracy of around 60%.

A PRIORI ELECTROCARDIOGRAPHIC CRITERIA

Table 4 shows the predictive accuracy of the QRS configuration classification based on published reports on leads V1 and V6. The predictive accuracy of V6 was very similar to that with the derived criteria at 66%. The high level of predictive accuracy for V1 (78%) was because this combined the criteria based on configuration and the criteria based on the initial R and S wave duration.

MULTIVARIATE ANALYSIS

Table 5 shows the results of multivariate analysis of the clinical data. Beta is the coefficient that is entered into the logistic regression equation. A history of myocardial infarction and an abnormal cardiothoracic ratio were the only independent predictors of the diagnosis of ventricular tachycardia.

Table 5 also shows the results of the multivariate analysis of the electrocardiographic data. The Kindwall criteria for "left bundle branch block" tachycardia; the specific waveforms in leads aVF, V1, and V6; and change in axis between sinus rhythm and tachycardia were independent predictors of ventricular tachycardia.

Table 5 also gives the results of multivariate

Table 2 QRS waveforms in the patients with either supraventricular tachycardia (SVT) or ventricular tachycardia (VT) analysed separately for "left bundle branch block" (LBBB) and "right bundle branch block" (RBBB) patterns

	I				*aVF*				*V1*				*V6*			
	LBBB		*RBBB*		*LBBB*		*RBBB*		*LBBB*		*RBBB*		*LBBB*		*RBBB*	
Waveform	*SVT*	*VT*	*SVT*	*VT*	*SVT*	*VT*	*SVT*	*VT*	*SVT*	*VT*	*SVT*	*VT*	*SVT*	*VT*	*SVT*	*VT*
1 R	12	16	1	2	6	12	4	5	0	0	2	12	10	15	4	1
2 Rs	1	1	5	8	4	0	2	1	0	0	2	4	2	4	8	5
3 rS	1	4	7	18	3	3	3	5	9	17	0	0	3	3	3	14
4 RSr	0	0	0	0	0	0	1	1	0	0	0	2	0	0	0	0
5 rSR	0	0	0	0	0	1	1	0	0	0	9	3	0	0	0	0
6 RsR	2	3	0	0	0	1	1	0	0	0	2	0	2	3	0	0
7 QS	0	5	2	3	4	15	1	16	8	14	0	0	0	2	1	12
8 qR	0	5	0	0	0	3	2	1	0	0	1	10	0	3	0	1
9 Qr	1	0	0	0	0	0	1	2	0	1	0	0	0	0	0	0
10 QRs	0	1	0	0	0	0	0	2	0	2	0	1	0	2	0	0
11 qRS	0	0	0	2	0	0	0	0	0	1	0	1	0	3	0	0
12 4X	0	0	1	1	0	0	1	1	0	0	0	1	0	0	0	1

Table 3 VT/SVT ratio in each lead and the assigned diagnosis of ventricular (VT) or supraventricular tachycardia (SVT) for "left bundle branch block" (LBBB) and "right bundle branch block" (RBBB) pattern tachycardias

		I				*aVF*				*V1*				*V6*			
		LBBB ratio/ diagnosis		*RBBB ratio/ diagnosis*		*LBBB ratio/ diagnosis*		*RBBB ratio/ diagnosis*		*LBBB ratio/ diagnosis*		*RBBB ratio/ diagnosis*		*LBBB ratio/ diagnosis*		*RBBB ratio/ diagnosis*	
Waveform																	
1	R	1 3	SVT	2	VT	2	VT	1 25	SVT	–	–	6	VT	1·5	SVT	0 25	SVT
2	Rs	1	SVT	1 6	SVT	*	SVT	0 5	SVT	–	–	2	VT	2	VT	0 6	SVT
3	rS	4	VT	2 6	VT	1	SVT	1 7	SVT	1 9	SVT	–	–	1	SVT	4 7	VT
4	RSr	–	–	–	–	–	–	1	SVT	–	–	–	–	*	SVT	–	–
5	rSR	–	–	–	–	†	VT	*	SVT	–	–	0 3	SVT	–	–	–	–
6	RsR	1 5	SVT	–	–	†	VT	*	SVT	–	–	*	SVT	1 5	SVT	–	–
7	QS	†	VT	1 5	SVT	3 8	VT	16	VT	1·8	SVT	–	–	†	VT	12	VT
8	qR	†	VT	–	–	†	VT	0·5	SVT	–	–	10	VT	†	VT	†	VT
9	Qr	*	SVT	–	–	–	–	2	VT	†	VT	–	–	–	–	–	–
10	QRs	†	VT	–	–	–	–	†	VT	†	VT	†	VT	†	VT	–	–
11	qRS	–	–	†	VT	–	–	–	–	†	VT	†	VT	†	VT	–	–
12	4X	–	–	1	SVT	–	–	1	SVT	–	–	†	VT	–	–	†	VT

*Only patients with SVT had this waveform in this lead; †only patients with VT had this waveform in this lead For waveforms see figure 2.

analysis of all the significant predictors, both clinical and electrocardiographic. A history of myocardial infarction, the specific QRS configurations in leads VI and aVF, and the change in axis from sinus rhythm to tachycardia remained independent predictors of ventricular tachycardia.

A repeat analysis was performed with only these four variables (table 6). Table 7 shows generated probabalistic functions. If none of the criteria was met then the diagnosis was almost certain to be supraventricular tachycardia. If only one criterion was met it was likely to be supraventricular tachycardia. If two criteria were met the diagnosis was likely to be ventricular tachycardia. If three or four of the criteria were met the diagnosis was almost certain to be ventricular tachycardia. Figure 6 shows the logistic curve generated by this analysis. The points on the curve for none, one, or two criteria present are plotted. With no criteria met then BX is $-6{\cdot}92$, the value of "constant", the constant term, and the probability of the diagnosis being ventricular tachycardia approaches zero. If the only criterion met is a myocardial infarction then $BX = -6{\cdot}92 + 6{\cdot}30 = -0{\cdot}62$ and so $P = 1/1+(e^{-BX}) = 1/1+(e^{0{\cdot}62}) = 0{\cdot}35$. The probability of the diagnosis being ventricular tachycardia is therefore 35% if the only criterion met is that the patient has had a past myocardial infarction. Applying these criteria back to the original data achieved a 93% predictive accuracy. This was increased to 95% by adding into the model independent P waves and ventricular extrasystoles with the same QRS configuration as in tachycardia. These tests will need to be repeated prospectively.

Table 8 shows the result of multivariate analysis using the a priori electrocardiographic classification, and the result when these were combined with the significant clinical variables. Table 9 is the final analysis with just the combined significant variables. Table 10 gives the generated probabilities as seen in table 7. When these criteria were applied back to the original data the predictive accuracy achieved was 84%.

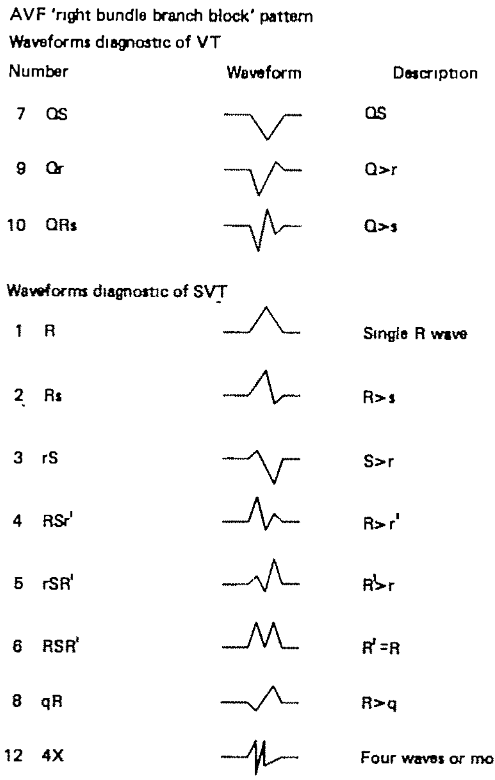


Figure 3 Predictive waveforms in lead aVF in "right bundle branch block" pattern tachycardia shown separately for ventricular and supraventricular tachycardia.

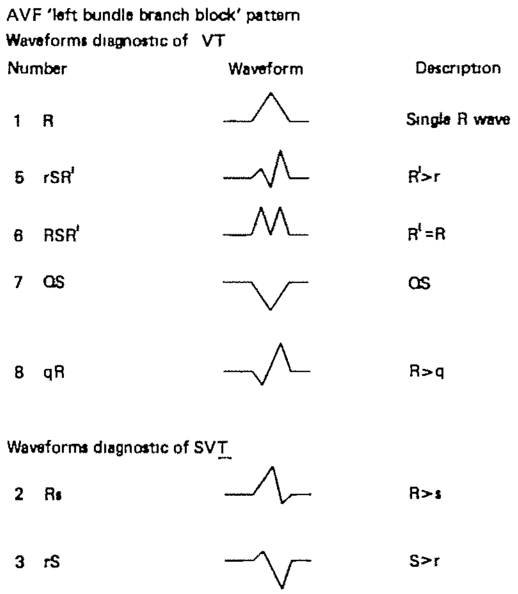
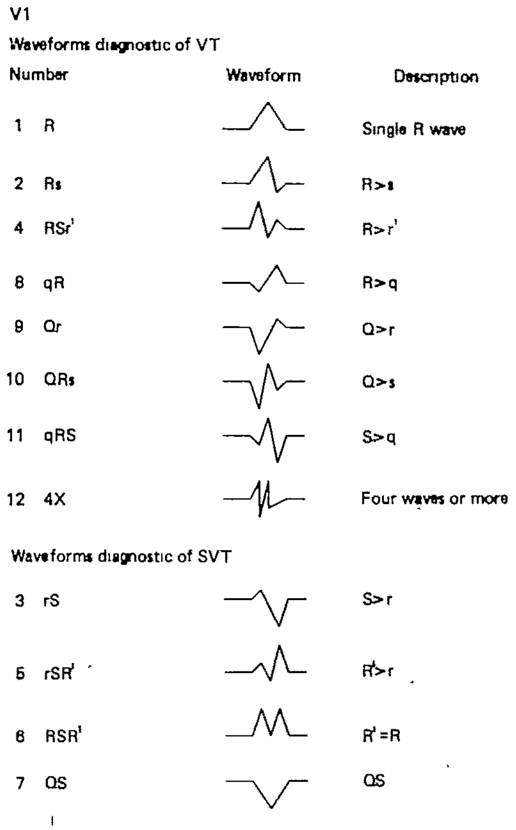

AVF 'left bundle branch block' pattern
Waveforms diagnostic of VT
Number
Waveform
Description
1 R
Single R wave
5 rSR'
R'>r
6 RSR'
R'=R
7 QS
QS
8 qR
R>q
Waveforms diagnostic of SVT
2 Rs
R>s
3 rS
S>r

Figure 4 Predictive waveforms in lead aVF in "left bundle branch block" pattern tachycardia shown separately for ventricular and supraventricular tachycardia.

Figure 5 Predictive waveforms in lead V1 shown separately for ventricular and supraventricular tachycardia.



Discussion

Previous investigators have identified many clinical and electrocardiographic criteria that are useful in the differential diagnosis of broad complex tachycardia. We have shown that many of these criteria are interrelated. The use of multivariate analysis allowed identification of the independent predictors in this study group.

We studied a series of consecutive patients referred for electrophysiological evaluation. The findings may not be directly applicable to all patients with broad complex tachycardias, but referral patterns probably reflect physician preference rather than patient selection. We therefore believe that these patients are broadly representative of those presenting to accident and emergency departments. Ideally, however, the results of this study need to be confirmed in a further prospective study, in which an attempt could be made to reduce further any selection bias. This has not been done with any previous study.

Table 4 Success of assigned waveforms and a priori waveforms in the diagnosis of ventricular tachycardia (VT) or supraventricular tachycardia (SVT)

Correct diagnosis in leads	*True diagnosis*		*Predictive power for VT*		
	VT	*SVT*	*Sensitivity (%)*	*Specificity (%)*	*Predictive Accuracy (%)*
		Success of assigned waveforms			
I	39/69	24/33	57	73	61
aVF	54/69	20/33	78	61	73
V1	35/69	28/33	51	85	62
V6	37/69	29/33	54	88	65
		Success of a priori waveforms			
V1	57/69	23/33	83	70	78
V6	41/69	26/33	59	79	66

Table 5 Multivariate analysis: constant is the constant term, β is the coefficient entered into the logit equation, and the p value is the significance of the variable

	β	*p value*
	Clinical variables alone	
Constant	−1·93	0·015
Age	0·027	0·19
MI	2·64	0·027
Hypotension	1·10	0·13
Smoking	0·589	0·36
CTR > 0·55	2·46	0·027
	Electrocardiographic criteria alone	
Constant	−4·65	0·185
Tachycardia:		
QRS width	−0·0089	0·65
RR interval	−0·0072	0·18
Configuration:		
Kindwall	2·56	0·0012
Lead I	0·345	0·67
Lead aVF	3·74	0·00041
Lead V1	3·39	0·0045
Lead V6	1·66	0·112
Axis tachycardia	0·46	0·59
Axis shift	3·42	0·000698
	Significant electrocardiographic and clinical variables	
Constant	−6·97	0·0002
MI	5·67	0·0034
CTR > 0·55	2·04	0·418
Kindwall	0·59	0·55
Lead aVF	4·32	0·00042
Lead V1	3·18	0·0026
Axis shift	2·21	0·00035

CTR, cardiothoracic ratio, MI, myocardial infarction.

Many of the results of univariate analysis in this study are in accord with previously published data. In the paper by Baerman and colleagues in 1987, an age greater than 35 years and a history of previous myocardial infarction, angina pectoris, or congestive cardiac failure all had positive predictive values of greater than 95% for the diagnosis of ventricular tachycardia.[3] In our study, smoking, haemodynamic collapse during the attack, and previous cardiac surgery were also associated with the diagnosis of ventricular tachycardia.

Many of the electrocardiographic criteria have been described before. The QRS width during tachycardia was described by Wellens and colleagues in 1978, who found that a width of greater than 140 ms predicted ventricular tachycardia.[4] In the present series five of the 33 patients with supraventricular tachycardia had a QRS width greater than 140 ms, either because of eccentric anterograde conduction through an accessory pathway (three patients) or an intraventricular conduction delay (two patients). Independent P waves are mentioned in all reports of the diagnosis of broad complex tachycardia. If correctly identified they are almost 100% specific for ventricular tachycardia with a high sensitivity (80–90%). Their identification on the electrocardiogram, however, is subjective and it is probably necessary to confirm the presence of independent atrial activity by some other method. Extrasystoles with the same QRS configuration as that seen during tachycardia were 100% specific for ventricular tachycardia, but only had a sensitivity of 17%.

Wellens and colleagues showed that left axis deviation in the presence of "right bundle branch block" pattern was a useful sign of ventricular tachycardia.[4] Dancy and Ward stated that left axis deviation during any broad

Table 6 Combined significant variables

	β	*p value*
Constant	−6·92	0·0003
MI	6·30	0·0009
Axis shift	4·45	0·00009
Lead aVF	4·53	0·00001
Lead V1	3·44	0·0009

MI, myocardial infarction

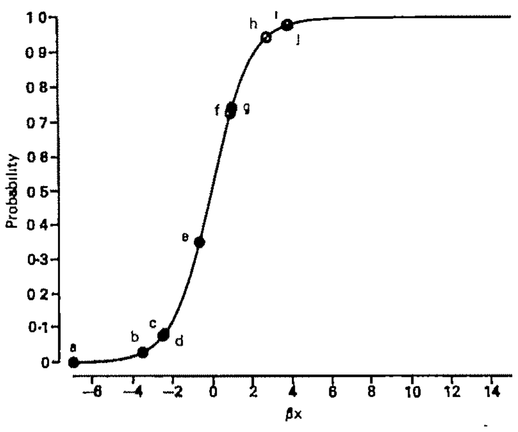


Figure 6 Logistic curve of BX (the sum of the equation) versus probability (the probability of the diagnosis being ventricular tachycardia) produced by the analysis with the points produced by the various combinations of the criteria met. The closed circles represent none or only one criterion present when the probability of the diagnosis of ventricular tachycardia is less than 50%. The open circles represent two criteria being present, and the probability of the diagnosis being ventricular tachycardia is greater than 50%. Three or four criteria make the probability of the diagnosis being ventricular tachycardia approach 100%. a = no criterion; b = V1; c = axis shift; d = aVF; e = MI; f = V1 + axis shift; g = V1 + aVF; h = MI + V1; i = MI + axis shift; j = MI + aVF.

complex tachycardia is indicative of ventricular tachycardia.[5] The present paper confirms both these observations, but also suggests that right axis deviation is an equally useful sign, especially in the presence of "left bundle branch block" pattern tachycardia. However, a change in axis between sinus rhythm and tachycardia of more than 40°, either to the right or to the left, was a more powerful predictor of ventricular tachycardia.

The paper by Dongas and colleagues suggested that an identical bundle block pattern in sinus rhythm and in tachycardia is diagnostic of supraventricular tachycardia.[6] However, only one patient with supraventricular tachycardia with bundle branch block both in sinus rhythm and in tachycardia was seen in this study. There were, however, two patients who had very similar "right bundle branch block" patterns in sinus rhythm and in ventricular tachycardia.

Previous papers have examined the configuration of the chest leads.[4 7] This study confirms that various waveforms in leads V1 and V6 in "right bundle branch block" pattern tachycardia are diagnostic. A single R wave or biphasic waveform in lead V1 was highly suggestive of ventricular tachycardia, while an RSR′ pattern was suggestive of supraventricular tachycardia unless the amplitude of the R wave was greater than that of the R′ wave. In lead V6 an R or RS pattern, where the R wave was greater in amplitude than the S wave, was suggestive of supraventricular tachycardia, while a Q wave or an RS pattern with a dominant S wave was suggestive of ventricular tachycardia. In this study lead I was not helpful in most patients, though in "left bundle branch block" pattern tachycardia a QS or qR was suggestive of ventricular tachycardia. Lead aVF was the most useful of the four leads, with a 72% predictive accuracy for ventricular tachycardia. In this lead a QS pattern was seen in 31/69 (45%) patients with ventricular tachycardia and only 5/33 (15%) patients with supraventricular tachycardia. The criteria for the analysis of "left bundle branch block" pattern tachycardia put forward by Wellens and colleagues and tested by Kindwall *et al* were also included in the multivariate analysis.[1 2]

When we tried to enter this data into multivariate analysis we encountered various problems. The main one was how to enter the different waveforms. The solution we used was to dichotomise them on the basis of the univariate analysis, so that waveforms seen more often with ventricular tachycardia or with supraventricular tachycardia were designated as being in favour of ventricular tachycardia or supraventricular tachycardia respectively. This method is not perfect, but alternative solutions such as converting each waveform, in each lead, to a risk ratio based on the proportion of VT/SVT has greater theoretical problems. It would convert non-continuous data to con-

Table 8 Multivariate analysis with a priori criteria

	β	*p value*
A priori electrocardiographic criteria alone		
Constant	−3·52	0·064
Tachycardia:		
QRS width	0·016	0·15
RR interval	−0·0036	0·41
Configuration:		
Lead V1	2·4	0·001
Lead V6	0·55	0·41
Axis tachycardia	0·61	0·33
Axis shift	2·05	0·0013
Significant a priori electrocardiographic and clinical variables		
Constant	−2·81	0·0024
MI	3·68	0·0028
CTR > 0·55	2·01	0·080
Lead V1	1·78	0·0087
Axis shift	2·34	0·0018

CTR, cardiothoracic ratio, MI, myocardial infarction

Table 7 Probabilities (%) that a broad complex tachycardia is ventricular in origin tested by the logistic regression equation if one or two of the four criteria are present

	Alone	*+MI*	*+Shift*	*+aVF*	*V1*
MI	35		98	98	95
Shift	8	98		88	72
aVF	8	98	88		74
V1	3	95	72	74	

If no criteria are met the probability that the diagnosis is ventricular tachycardia is less than 1%. If three or four criteria are met the probability that the diagnosis is ventricular tachycardia is greater than 99%.
MI, myocardial infarction.

Table 9 Combined significant variables

	β	p value
Constant	−2·73	0·0002
MI	3·86	0·001
Axis shift	2·55	0·00043
Lead V1	1·87	0·0049

MI, myocardial infarction.

tinuous data and would make the clinical use of the criteria even more difficult. The waveform criteria in leads V1 and V6 which were used for the diagnosis of "right bundle branch block" pattern tachycardias as described by Wellens and colleagues[4] are essentially the same as those generated by this study but they cannot be used alone because they do not include all possible waveforms. Because of the theoretical problems of deriving the electrocardiographic criteria from the data we also tested an a priori classification of leads V1 and V6. This showed that lead V1, but not lead V6, was an important independent predictor of the origin of a broad complex tachycardia, with similar waveform criteria as the derived classification. Concordance, either negative or positive, across the chest leads was not analysed separately from waveforms in leads V1 or V6 because it would be a derivative variable. Axis and axis change were dichotomised because the circular nature of the axis does not allow their use as continuous variables.

The second problem was that of variables that were obviously dependent on each other. The multivariate model we used was based on the premise that the variables show some independence. This means that the very dependent variables must be eliminated. Because all patients with angina, coronary artery surgery, or congestive heart failure had had either a myocardial infarction or an abnormal cardiothoracic ratio or both we did not enter these variables into the multivariate analysis. Independent P waves and identical ventricular extrasystoles posed a different problem. Both these variables in this data set were 100% specific. In iterations the model found that these variables were always associated with ventricular tachycardia but with a low sensitivity and so they had no effect on the predictive power of the other variables. These two variables, therefore, produced a very high coefficient (β) and a P value approaching unity. When they were added to the final analysis these two variables increased the diagnostic accuracy of the model from 93% to 95%.

In the present study the analysis of the electrocardiograms was not performed blindly. The validity of the relatively soft sign of independent P waves was not adequately tested and would therefore benefit from further research. As with previous studies,[1,5,7] blinding the observer to the other electrocardiographic signs was not thought necessary because these criteria were all objective measurements.

Table 10 Probabilities (%) that a broad complex tachycardia is ventricular in origin tested by the logistic regression equation if one or two of the four criteria are present

	Alone	+MI	+Shift	V1
MI	75		97	95
Shift	45	97		85
V1	29	95	85	

If no criteria are met the probability that the diagnosis is ventricular tachycardia is less than 1%.
If three or four criteria are met the probability that the diagnosis is ventricular tachycardia is greater than 99%.
MI, myocardial infarction.

Our multivariate analysis showed the interdependence of many of the clinical and electrocardiographic features. A history of myocardial infarction and an abnormal cardiothoracic ratio were two independent clinical predictors of ventricular tachycardia. The QRS patterns in leads aVF, V1, and V6, as well as the criteria of Kindwall and colleagues and the change in QRS axis were all independent electrocardiographic predictors of ventricular tachycardia. When the electrocardiogram and clinical data were added together the independent predictors were a history of myocardial infarction, the QRS complex configurations in leads aVF and V1, and change in QRS axis. Thus the criteria of Kindwall and colleagues did not seem to be independent of a history of myocardial infarction.[2] QRS complex configuration in lead V6 was not an independent predictor of ventricular tachycardia, though it is widely used.[4] The QRS configuration in lead aVF was an important independent preditor of the origin of the tachycardia. Lead aVF has not been previously analysed in this context and these findings need confirmation.

The four independent variables when applied back to the data achieved a 93% predictive accuracy (dropping to 84% if only an a priori electrocardiographic classification is used). The addition of the two very specific variables, ventricular extrasystoles of the same configuration and independent P waves, increases the diagnostic accuracy of the model by only 2%. The fact that the predictive accuracy did not approach 100% supports the use of other methods as adjuncts to the diagnosis. Attempted termination by adenosine and Doppler analysis of the atrioventricular relation may allow more accurate analysis.[12,13] The use of adjunctive diagnostic methods is particularly important if only one or two major diagnostic criteria are met because the diagnosis is then still in doubt (with probabilities of 3–35% or 72–98% respectively for the diagnosis of ventricular tachycardia). The diagnosis is virtually certain if either none (supraventricular tachycardia) or three or four criteria are met (ventricular tachycardia). A computer based expert system using these four criteria would be extremely useful in clinical practice. Alternatively, these criteria could form the basis of a simple clinical algorithm, which could be made available in accident and emergency departments.

The analysis using the a priori criteria confirms that lead V1, axis shift, and a history of a myocardial infarction are the three independent predictive variables. Their combined predictive accuracy of 84% is lower than that seen with the derived electrocardiographic criteria, probably because of the exclusion of lead aVF.

We found that a history of myocardial infarction, axis shift during tachycardia, and the QRS configuration in lead V1 were the independent predictors of the origin of a broad complex tachycardia. The QRS configuration in lead aVF also seems to be both an important univariate and independent multivariate predictor of the origin of a broad complex tachycardia, but this needs prospective confirmation.

The statistics in this study were performed in conjunction with John Micklewright, PhD, lecturer in microeconometrics at Queen Mary's College and Associate Professor, University of Florence. His specialty is the application of statistics to small population groups.

1 Wellens HJJ, Brugada P. Diagnosis of ventricular tachycardia from the twelve lead electrocardiogram *Cardiol Clin* 1987;5·511–26
2 Kindwall EK, Brown J, Josephson ME. Electrocardiographic criteria for ventricular tachycardia in wide complex left bundle branch block morphology tachycardia. *Am J Cardiol* 1988;61.1279–83.
3 Baerman JF, Morady F, DiCarlo LA, de Buitler M Differentiation of ventricular from supraventricular tachycardia with aberration value of the clinical history *Ann Emerg Med* 1987,16 40–3
4 Wellens HJJ, Bar FWHM, Lie KI The value of the electrocardiogram in the differential diagnosis of a tachycardia with a widened QRS complex. *Am J Med* 1978;64·27–33.
5 Dancy M, Ward DE. Clinical algorithm for the diagnosis of ventricular tachycardia. *BMJ* 1985;291.1036–9.
6 Dongas J, Lehmann MH, Mahmud R, Denker S, Soni J, Akhtar M. The value of pre-existing bundle branch block in the electrocardiographic differentiation of supraventricular from ventricular origin of wide complex tachycardia. *Am J Cardiol* 1985,55 717–21.
7 Marriott HJL, Sandler IA. Criteria, old and new, for differentiating between ectopic ventricular beats and aberrant ventricular conduction in the presence of atrial fibrillation *Prog Cardiovasc Dis* 1966;9.18–28
8 Tchou P, Young P, Mahmud R, Denker S, Jazayeri M, Akhtar M. Useful clinical criteria for the diagnosis of ventricular tachycardia. *Am J Med* 1988,84:53–6
9 Melfi CA Limdep: a review *Journal of Applied Econometrics* 1987;2:251–5.
10 Diamond GA, Pollock BH, Work JW. Clinical decisions and computers *J Am Coll Cardiol* 1987,9 1385–96
11 Willems JL, Lesaffre E Comparison of multigroup logistic and linear discriminant ECG and VCG classification. *J Electrocardiol* 1987,20 83–92.
12 Griffith MJ, Linker NJ, Ward DE, Camm AJ. Adenosine in the diagnosis of broad complex tachycardias. *Lancet* 1988;i.672–5
13 Griffith MJ, Mehta D, Ward DE, Camm AJ. Doppler diagnosis of broad complex tachycardias *Am Heart J* 1988,116·555–7.

NOTICES

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The **Fourth Annual International Symposium on New Technologies in Cardiovascular Ultrasound** will be held at the Mayo Clinic, Rochester, Minnesota, USA, on 15 to 18 September (Satellite Teleconference: Mayo Jacksonville, Mayo Scottsdale, Sao Paulo, Brazil, and Buenos Aires, Argentina): Fax 507 284 0532; Tel 507 284 2509 or 1 800 323 2688.

The **Fifth International Workshop on Future Directions in Interventional Cardiology** will be held in Santa Barbara, California, on 20 to 22 September: The American College of Cardiology, 9111 Old Georgetown Road, Bethesda, MD 20814, USA (Fax: 301 897 9745; Tel: 301 897 2695).

The **Third International Workshop on Magnetic Resonance Angiography** will be held in L'Aquila on 13 October: Scientific Secretariat, Dr Paolo Pavone, Department of Radiology, University of L'Aquila, Ospedale Collemaggio, 67100 L'Aquila, Italy (Fax: 39 862 410997; Tel: 39 862 26164).

The **First Symposium on Magnetic Resonance Imaging of the Cardiovascular System** will be held in Rome on 14 to 16 October: Scientific Secretariat, Dr Paolo Pavone, Department of Radiology, University of L'Aquila, Ospedale Collemaggio, 67100 L'Aquila, Italy (Fax: 39 862 410997; Tel: 39 862 26164).

An **International Symposium and Workshop on Transoesophageal Echocardiography in Congenital Heart Disease** will be held in Edinburgh on 23 and 24 November: The Secretary, Symposium "TEE in Congenital Heart Disease", Department of Paediatric Cardiology, Royal Hospital for Sick Children, Sciennes Road, Edinburgh EH9 1LF.

1992

The Annual Meeting of the **British Cardiac Society** will take place at the Harrogate International Centre on 26 to 29 May.

The **Ninth International Congress of Histochemistry and Cytochemistry** will be held in Maastricht on 30 August to 5 September: Organising Secretariat, Professor F C S Ramaekers, Department of Molecular Cell Biology, University of Limburg, PO Box 616, 6200 MD Maastricht, The Netherlands (Fax: 31 43 437640; Tel: 31 43 888642).

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Comparison between prostaglandin E_1 and epoprostenol (prostacyclin) in infants after heart surgery

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Abstract

***Objective*—To study the dose response characteristics of prostaglandin E_1 and epoprostenol (prostacyclin) and directly to compare their effectiveness as pulmonary vasodilators in infants with pulmonary hypertension.**

***Design*—A crossover design with each patient receiving both drugs in random order.**

***Setting*—Infants were studied in the intensive care unit while they were sedated, paralysed, and ventilated.**

***Patients*—Twenty infants who had undergone corrective cardiac surgery and who were in sinus rhythm, had stable haemodynamic function, and had a pulmonary artery catheter in place. All infants were receiving dopamine and phenoxybenzamine.**

***Interventions*—Baseline haemodynamic measurements were taken and an infusion of the first drug was started at the lowest dose: after 20 minutes the measurements were repeated and the dose increased. This protocol was repeated for all doses of both drugs: 10, 30, and 100 ng/kg/min of prostaglandin E_1 and 5, 10, and 25 ng/kg/min of epoprostenol. Cardiac output was measured by the pulsed Doppler ultrasound method.**

***Main outcome measures*—Pulmonary and systemic vascular resistances were calculated from the cardiac output and compared by the Wilcoxon signed ranks test.**

***Results*—Both prostaglandin E_1 and epoprostenol were effective vasodilators: 5 ng/kg/min of epoprostenol was equivalent to 30 ng/kg/min of prostaglandin E_1.**

***Conclusions*—Neither drug showed pulmonary specificity.**

Prostaglandin E_1 and epoprostenol (prostacyclin, PGI_2) are endogenous prostaglandins with potent vasodilatory effects and similar structures and properties.[1,2] PGE_1 was the first prostaglandin to be isolated.[1,2] It is used as a pulmonary vasodilator in patients with pulmonary hypertension[3,4] and though the pulmonary circulation can rapidly metabolise PGE_1[5] systemic vasodilatation often accompanies doses large enough to cause pulmonary vasodilatation.[4] It is used extensively to maintain ductal patency in infants with congenital heart disease who are ductus dependent,[6] but there are few published reports of its use as a pulmonary vasodilator in infants and children.[7,8]

Prostacyclin, identified in 1976, is the main arachidonic acid metabolite formed by vascular endothelium.[2] It is a more potent inhibitor of platelet aggregation than PGE_1 and may also play a part in modulating pulmonary vascular tone, thereby contributing to the thromboresistance of endothelial cells.[2] Early reports of its use in children suggested that it caused highly selective pulmonary vasodilatation[9,10]; however, in larger studies PGI_2 was a consistent but non-selective vasodilator.[11–13] As epoprostenol, prostacyclin is used clinically both to assess the reversibility of pulmonary vasoconstriction before surgery[11,14] and as long term treatment for patients with primary pulmonary hypertension.[15]

In infants with cardiac lesions associated with high pulmonary blood flow severe pulmonary vasoconstriction can develop in response to adverse factors after operation.[16,17] PGE_1 and epoprostenol are both used in the management of reactive pulmonary hypertension but there is no reported comparison of their efficacy in infants. This study was conducted to document the dose response characteristics of PGE_1 and epoprostenol and directly to compare their effectiveness as pulmonary vasodilators.

Patients and methods

PATIENTS

The mean age of the 20 patients we studied was 2·8 months (range 3 days–6 months), and their mean weight was 4·2 kg (3·2–6·2 kg). The diagnoses were ventricular septal defect (nine cases), complete atrioventricular canal (five cases), total anomalous pulmonary veins (four cases), transposition of the great vessels (one case), and truncus arteriosus (one case).

METHODS

The study was carried out in the Intensive Care Unit at the Royal Children's Hospital, a multidisciplinary unit that has 600 cardiac surgical admissions a year. Patients undergoing intracardiac repair were eligible for the study if they were less than 12 months old, in sinus rhythm, had no bleeding, showed less than 5% change in cardiovascular variables over the previous hour, and had a pulmonary artery catheter in place. Informed parental consent and the approval of the ethics committee were obtained. Patients were studied 4–48 hours after operation and were given a morphine infusion (10–30 μg/kg/h), neuromuscular blockade with pancuronium (0·1 mg/kg as required), inotropic treatment (dopamine 5–10 μg/kg/min), and vasodilatation with intravenous phenoxybenzamine (1 mg/kg as a loading dose intraoperatively, then 0·5–1 mg/kg every 8–12 hours). The dopamine infusion rate, arterial pH, and $Paco_2$ were held constant during the study.

Monitoring included continuous heart rate, mean systemic and pulmonary arterial pressures, and right and left atrial pressures, measured via catheters placed at operation. The cardiac output was measured non-invasively by the pulsed Doppler ultrasound method[18] with a Vingmed SD-100 unit (Vingmed Horten, Horten, Norway). PGE_1 (Prostin VR Pediatric, Upjohn, Kalamazoo, MI 49001, USA) was diluted in 0·9% saline solution; epoprostenol (Flolan, Wellcome, UK) was diluted in glycine buffer and then 0·9% saline according to the manufacturer's instructions. The drugs were infused into a central or peripheral intravenous line by a syringe pump. The doses of PGE_1 used were 10, 30, and 100 ng/kg/min, and the doses of epoprostenol were 5, 10, and 25 ng/kg/min.

We studied 20 patients; each received an infusion of PGE_1 and epoprostenol given in random order. After baseline measurements were taken an infusion of the first drug was started at the lowest dose; after 20 minutes the measurements were repeated and the infusion rate was increased. This sequence was repeated for each dose of the first drug and then for the other drug, allowing a washout period of 20 minutes. Each drug infusion was started at the lowest dose because of the risk of systemic hypotension. Colloid was given if required to keep left atrial pressure constant.

Derived variables were calculated according to the following formulas: cardiac index (l/min/m^2) = cardiac output (l/min)/body surface area (m^2); systemic vascular resistance (dyn.s.cm^{-5}) = (mean systemic arterial pressure − right atrial pressure) × 79·9/cardiac output; pulmonary vascular resistance (dyn.s.cm^{-5}) = (pulmonary artery pressure − left atrial pressure) × 79·9/cardiac output.

We used the Wilcoxon signed ranks test to compare the haemodynamic values at each dose of the drugs with baseline values and to compare the effects of one drug with those of the other.

Results

Table 1 shows the effects of PGE_1 on the haemodynamic indices and table 2 the effects of epoprostenol on the haemodynamic indices.

Both drugs produced a decrease in pulmonary and systemic vascular resistance (figs 1 and 2) and an increase in the cardiac index (fig 3); PGE_1 at 30 and 100 ng/kg/min produced vasodilatation approximately equal to that produced by 5 and 10 ng/kg/min of epoprostenol respectively. Neither drug, however, showed any specificity for the pulmonary circulation. To compare their degree of pulmonary specificity we calculated a quantitative value of the relative effects of PGE_1 and epoprostenol from the absolute differences between the change in the pulmonary and systemic vascular resistances from control values at each dose. These differences for equivalent doses were then compared by the Wilcoxon signed ranks

Table 1 Effects of prostaglandin E_1 (PGE_1) infusion on haemodynamic indices in 20 infants (mean (SD))

		Dose of PGE_1		
Index	*Control (n = 20)*	*10 ng/kg/min (n = 20)*	*30 ng/kg/min (n = 20)*	*100 ng/kg/min (n = 20)*
HR (beats/min)	156 (18)	161 (20)*	159 (16)	158 (16)
MAP (mm Hg)	54·4 (8·0)	53·9 (9·9)	52·0 (8·1)*	50·8 (9·1)*
PAP (mm Hg)	21·3 (5·1)	21·2 (5·4)	20·4 (4·4)*	19·5 (4·8)*
LAP (mm Hg)	8·0 (2·0)	8·2 (2·1)	7·9 (1·9)	7·8 (1·9)
RAP (mm Hg)	6·2 (2·0)	6·4 (2·2)	6·3 (2·0)	6·3 (2·4)
CI (l/min/m^2)	4·2 (1·3)	4·3 (1·3)	4·4 (1·4)*	4·5 (1·4)*
SVR (dyn s cm^{-5})	3793 (1153)	3622 (1017)	3427 (1029)*	3312 (1060)*
PVR (dyn.s.cm^{-5})	1075 (576)	1027 (514)*	968 (483)*	880 (425)*

*p < 0·05 (compared with control values).
CI, cardiac index, HR, heart rate; LAP, left atrial pressure; MAP, mean systemic arterial pressure, PAP, pulmonary arterial pressure, PVR, pulmonary vascular resistance; RAP, right atrial pressure, SVR, systemic vascular resistance.

Table 2 Effects of epoprostenol (PGI_2) infusion on haemodynamic indices in 20 infants (mean (SD))

		Dose of PGI_2		
Index	*Control (n = 20)*	*5 ng/kg/min (n = 20)*	*10 ng/kg/min (n = 20)*	*25 ng/kg/min (n = 15)*
HR (beats/min)	156 (18)	162 (17)*	162 (16)*	168 (18)*
MAP (mm Hg)	54·4 (8·0)	54·2 (10·7)	50·2 (10·6)*	46·7 (9·4)*
PAP (mm Hg)	21·4 (4·9)	21·3 (5·2)	20·1 (4·6)*	19·7 (4·4)*
LAP (mm Hg)	8·0 (2·0)	8·4 (2·1)	8·4 (2·4)	8·3 (2·5)
RAP (mm Hg)	6·2 (2·1)	6·4 (2·3)	6·7 (2·2)*	6·9 (1·9)*
CI (l/min/m^2)	4·2 (1·3)	4·4 (1·3)*	4·6 (1·3)*	5·3 (1·6)*
SVR (dyn s cm^{-5})	3875 (1227)	3584 (1176)*	3084 (982)*	2438 (757)*
PVR (dyn s.cm^{-5})	1100 (551)	996 (479)*	857 (382)*	702 (276)*

*p < 0·05 (compared with control values) See footnote to table 1 for abbreviations

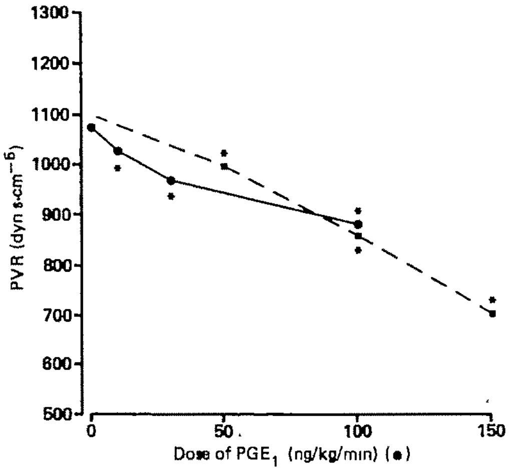

Figure 1 Effects of prostaglandin E_1 (PGE_1) and epoprostenol (PGI_2) on pulmonary vascular resistance (PVR). $^*p < 0.05$, for change from control values.

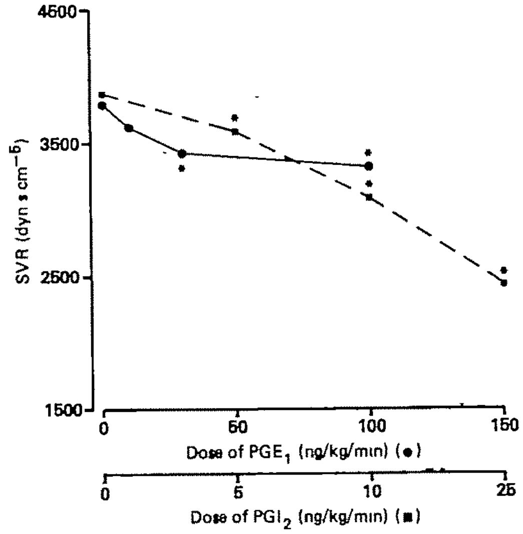

Figure 2 Effects of prostaglandin E_1 (PGE_1) and epoprostenol (PGI_2) on systemic vascular resistance (SVR). $^*p < 0.05$, for change from control values.

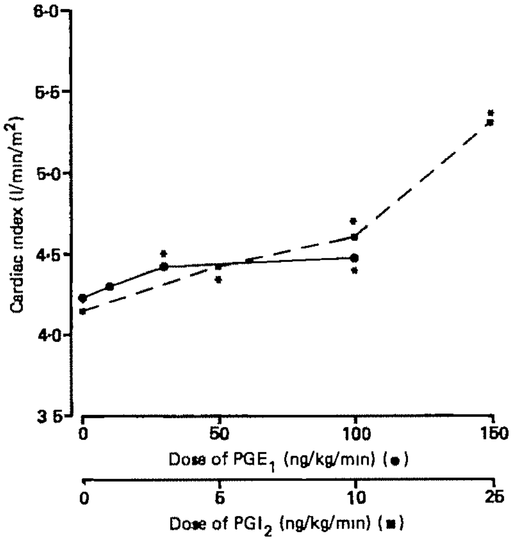

Figure 3 Effects of prostaglandin E_1 (PGE_1) and epoprostenol (PGI_2) on cardiac index. $^*p < 0·05$, for change from control values.

test; they did not reach statistical significance—that is, no difference was shown between the pulmonary specificity of the two drugs.

Discussion

We confirmed that both PGE_1 and epoprostenol are effective vasodilators, producing a decrease in systemic and pulmonary vascular resistances, but with no pulmonary specificity. Epoprostenol was 6–10 times more potent than PGE_1.

Haemodynamic function can change considerably as the circulation recovers from cardiopulmonary bypass. To minimise the effects of this we used each patient as his own control, randomised the order of the drugs, and limited each infusion period to 20 minutes. In our unit inotropic treatment (dopamine 5–10 μg/kg/min) and phenoxybenzamine are given routinely to infants after cardiopulmonary bypass. Dopamine at these doses may increase cardiac index and systemic pressure but does not significantly alter pulmonary artery pressure or the pulmonary vascular resistance.[19 20] Phenoxybenzamine, a direct α adrenergic blocking agent,[21] vasodilates all vascular beds; it is not known how this affects the actions of PGE_1 and epoprostenol and therefore our results may not be valid for patients who are not taking α adrenergic blocking agents.

Cardiac output measured by pulsed Doppler ultrasound accords closely with the results obtained by the Fick and dye dilution techniques in infants[18 22]; the technique is simple, non-invasive, can be performed repeatedly, and is used in our unit as the standard measure of cardiac output. None of the potential sources of error such as aortic valve abnormalities, subcutaneous emphysema, or a significant intracardiac shunt were present in the patients we studied.

Rubis *et al* compared the effects of PGE_1 in children after open-heart surgery with those of sodium nitroprusside.[7] Although both PGE_1 and sodium nitroprusside were effective vasodilators, PGE_1 produced a more variable response: high doses of PGE_1 (200–1000 ng/kg/min) produced troublesome side effects in five of their 26 patients, four of whom had an increase in pulmonary and systemic pressures. We used lower doses of PGE_1 in a younger, more homogeneous population, and all patients were sedated, ventilated, and receiving inotropic treatment. These factors probably explain the lack of adverse effects and the consistent vasodilatation we observed. The effects of epoprostenol in our patients accord with those reported in older children and adults: Bush *et al* studied the effects of epoprostenol in 20 children aged 2 months to 19 years with pulmonary hypertension caused by congenital heart disease, and showed a dose-dependent but non-selective vasodilatation.[23] In their study systemic hypotension occurred at doses higher than 20 ng/kg/min.

PGE_1 and epoprostenol were equally effective in infants with pulmonary hypertension after cardiac surgery. Because epoprostenol is more expensive, we believe that PGE_1 is the preferred drug. As more is learned about the specific roles of the prostaglandins in the pathophysiology of pulmonary vascular disease, however, epoprostenol may become the drug of choice.

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1 Moncada S, Flower RJ, Vane JR. Prostaglandins, prostacyclin, thromboxane A_2, and leukotrienes In: Gilman AG, Goodman LS, Rall TW, Murad F, eds. *Goodman and Gilman's the pharmacological basis of therapeutics* 7th ed New York· Macmillan, 1985 660–73.
2 Vane JR. Adventures and excursions in bioassay—the stepping stones to prostacyclin. *Postgrad Med J* 1983;59. 743–58.
3 Szczeklik J, Dubiel JS, Mysik M, Pyzik Z, Krol R, Horzela T Effects of prostaglandin E_1 on pulmonary circulation in patients with pulmonary hypertension. *Br Heart J* 1978;40 1397–401.
4 D'Ambra MN, LaRaia PJ, Philbin DM, Watkins WD, Hilgenberg AD, Buckley MJ Prostaglandin E_1: a new therapy for refractory right heart failure and pulmonary hypertension after mitral valve replacement *J Thorac Cardiovasc Surg* 1985;89·567–72.
5 Piper PJ, Vane JR, Wyllie JH. Inactivation of prostaglandins by the lungs. *Nature* 1970;225 600–4
6 Freed MD, Heymann MA, Lewis AB, Roehl SL, Kensey RC. Prostaglandin E_1 in infants with ductus arteriosus-dependent congenital heart disease. *Circulation* 1981; 64:899–904.
7 Rubis LJ, Stephenson LW, Johnston MR, Nagaraj S, Edmunds LH Comparison of effects of prostaglandin E_1 and nitroprusside on pulmonary vascular resistance in children after open-heart surgery *Ann Thorac Surg* 1981;32.563–70
8 Swan PK, Tibballs J, Duncan AW. Prostaglandin E_1 in primary pulmonary hypertension. *Crit Care Med* 1986; 14:72–3.
9 Watkins WD, Peterson MB, Crone RK, Shannon DC, Levine L Prostacyclin and prostaglandin E_1 for severe idiopathic pulmonary artery hypertension [Letter] *Lancet* 1980;i 1083.
10 Lock JE, Olley PM, Coceani F, Swyer PR, Rowe RD Use of prostacyclin in persistent fetal circulation [Letter] *Lancet* 1979;ii.1343.
11 Bush A, Busst CM, Knight WB, Shinebourne EA Comparison of the haemodynamic effects of epoprostenol (prostacyclin) and tolazoline. *Br Heart J* 1988,60.141–8.
12 Szczeklik J, Szczeklik A, Nizankowski R Haemodynamic changes induced by prostacyclin in man *Br Heart J* 1980;44:254–8.
13 Groves BM, Rubin LJ, Frosolono MF, Cato AE, Reeves JT. A comparison of the acute hemodynamic effects of prostacyclin and hydralazine in primary pulmonary hypertension. *Am Heart J* 1985,110:1200–4.
14 Rozkovec A, Stradling JR, Shepherd G, MacDermot J, Oakley CM, Dollery CT. Prediction of favourable responses to long term vasodilator treatment of pulmonary hypertension by short term administration of epoprostenol (prostacyclin) or nifedipine. *Br Heart J* 1988,59·696–705.
15 Rubin LJ, Mendoza J, Hood M, *et al.* Treatment of primary pulmonary hypertension with continuous intravenous prostacyclin (Epoprostenol) *Ann Intern Med* 1990; 112:485–91.
16 Perkin RM, Anas NG. Pulmonary hypertension in pediatric patients. *J Pediatr* 1984;105·511–22
17 Burrows FA, Klinck JR, Rabinovitch M, Bohn DJ Pulmonary hypertension in children: perioperative management *Can Anaesth Soc J* 1986,33:606–28.
18 Alverson DC. Neonatal cardiac output measurement using pulsed Doppler ultrasound. *Clin Perinatol* 1985,12· 101–27.
19 Lang P, Williams RG, Norwood WI, Castaneda AR The hemodynamic effects of dopamine in infants after corrective cardiac surgery. *J Pediatr* 1980;96:630–4
20 Stephenson LW, Edmunds LH, Raphaely R, Morrison DF, Hoffman WS, Rubis LJ Effects of nitroprusside and dopamine on pulmonary arterial vasculature in children after cardiac surgery. *Circulation* 1979,60(suppl I): 104–10.
21 Weiner N Drugs that inhibit adrenergic nerves and block adrenergic receptors. In. Gilman AG, Goodman LS, Rall TW, Murad F, eds. *Goodman and Gilman's the pharmacological basis of therapeutics* 7th ed New York Macmillan, 1985:181–214
22 Tibballs J, Osborne A, Hochmann M A comparative study of cardiac output measurement by dye dilution and pulsed Doppler ultrasound *Anaesth Intensive Care* 1988,16 272–7.
23 Bush A, Busst C, Booth K, Knight WB, Shinebourne EA Does prostacyclin enhance the selective pulmonary vasodilator effect of oxygen in children with congenital heart disease? *Circulation* 1986;74 135–44

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CASE REPORTS

Thrombus within a submitral left ventricular aneurysm: diagnosis on cross sectional echocardiography

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Abstract
Subvalvar left ventricular aneurysms are rare and occur predominantly in black Africans. A submitral left ventricular aneurysm was diagnosed on cross sectional echocardiography in a black woman born in the United Kingdom. The left parasternal long axis view showed a highly echogenic mass apparently attached to the wall of a dilated left atrium, but the apical two-chamber view showed that this was thrombus in the apex of a left ventricular aneurysm. The patient subsequently underwent surgical correction.

Subvalvar left ventricular aneurysms are rare. They occur predominantly in the black races of sub-Saharan and Western Africa with sporadic cases in North America, the West Indies, and Japan. They arise most commonly in relation to the mitral valve annulus and may contain thrombus. We report an example of a submitral aneurysm in a black woman born in the United Kingdom. To our knowledge this is only the second report of such a case in the United Kingdom and the first in which the appearance of thrombus within the aneurysm was shown by cross sectional echocardiography.

Case report

A 24 year old black woman was admitted with a two year history of dyspnoea. She was born in Britain. Her mother was also black and from Sierra Leone but the ethnic origin of her father was not known. Dyspnoea initially developed while she was visiting Sierra Leone, where rheumatic mitral valve disease was diagnosed. There was no prior history of rheumatic fever. She was treated with digoxin and diuretics with symptomatic improvement. She had stopped these five months before admission and in the month before admission progressive dyspnoea, orthopnoea, fatigue, and paroxysmal nocturnal dyspnoea had again developed.

Physical examination showed a pulse rate of 120 beats per minute in atrial fibrillation and blood pressure of 120/60 mm Hg. The jugular venous pressure was raised to 3 cm above the sternal angle. The apex beat was displaced 2 cm lateral to the mid-clavicular line and was hyperdynamic. A grade two pansystolic murmur was audible at the apex and radiated to the left axilla. Crackles were audible to the mid-zones of the chest bilaterally.

An electrocardiogram confirmed atrial fibrillation and showed borderline left ventricular hypertrophy but was otherwise within normal limits. A chest radiograph showed cardiomegaly with a cardiothoracic ratio of 14/22. There was a double right heart border with straightening of the left heart border. The lung fields showed pulmonary oedema.

Cross sectional echocardiography in the left parasternal long axis view showed a highly echogenic mass apparently attached to the wall of a dilated left atrium (5·0 cm). In the apical two-chamber view, however, this was identified as clot in the apex of a left ventricular aneurysm filling half its cavity (fig 1). The aneurysm arose below the posterior mitral valve leaflet and extended to compress the left atrium from behind, stretching the posterior leaflet of the mitral valve. The valve leaflets showed mild thickening and there was evidence of moderate mitral regurgitation on colour flow Doppler mapping.

The findings on cardiac catheterisation accorded with those on echocardiography, the

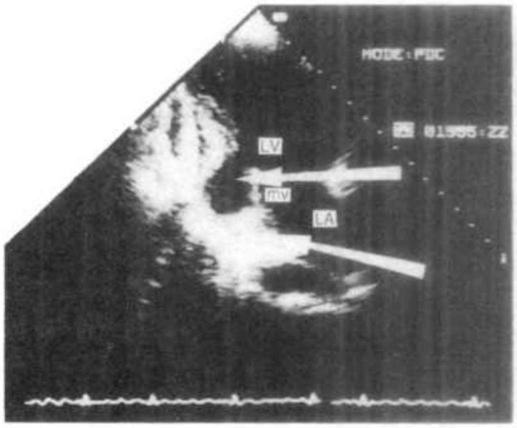


Figure 1 Cross sectional echocardiogram in the apical two-chamber view showing the aneurysm cavity (upper arrow) arising from the left ventricle immediately below the posterior mitral valve leaflet. It contained thrombus (lower arrow) and indented the left atrium. LV, left ventricle; mv, mitral valve; LA, left atrium.

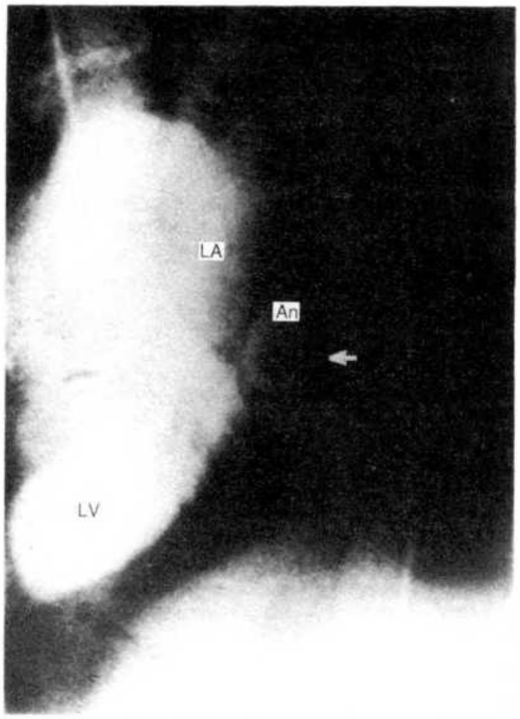


Figure 2 Left ventricular cineangiogram in the lateral view showing the aneurysm containing thrombus which appeared as a filling defect (arrow). It arose below the left atrium which was filled by mitral valve regurgitation and was displaced superiorly. An, aneurysm; LV, left ventricle; LA, left atrium.

aneurysm being best defined in the lateral view. On left ventricular cineangiography two cavities filled posterior to the left ventricle (fig 2). On pulmonary artery injection with follow through the upper of these was identified as the left atrium (filling before the left ventricle) and the lower as the aneurysm (filling from the left ventricle), which contained thrombus and compressed the left atrium from below. The coronary arteries appeared normal.

She improved after treatment with digoxin and diuretics was restarted. Subsequent chest radiographs, however, showed right upper lobe infiltration and there were acid fast bacilli in her sputum. After four months of antituberculous chemotherapy she underwent successful repair of the aneurysm. The posterior leaflet of the mitral valve was extensively reconstructed and the thrombus removed.

Two months later she was readmitted with severe mitral regurgitation. At reoperation there was considerable fibrosis of the posterior leaflet and its chordal apparatus. This produced retraction of the leaflet into the left ventricular cavity and relative prolapse of the anterior leaflet. The rigidity of the annulus precluded further repair and a xenograft was inserted. She has subsequently been well.

Discussion

Left ventricular aneurysms in white patients are almost invariably associated with coronary artery disease; however, a peculiar form that is both morphologically and aetiologically different occurs in black patients. These differences were first recognised in South Africans by Jacobs and Elliott.[1] They noted that whereas coronary artery disease was present in all of 57 consecutive patients of European descent with left ventricular aneurysms it was absent in 15 consecutive patients from Bantu tribes. They also noted that the posterior wall was the most common site of the aneurysm in those of Bantu origin. Subsequently, Abrahams *et al* described the association with the mitral and aortic valve rings, the former being the more common.[2] Patients have since been described with aneurysms arising at the left ventricular apex. The cause of this condition remains obscure though a congenital weakness in the ventricular wall seems most likely.

Most cases occur in sub-Saharan Africa but even there this condition is rare with an incidence of 0·02% in Zaire, the source of the largest number of reports.[3] The only case previously reported in this country was in a white patient; however, he had electrocardiographic changes suggestive of previous posterior infarction and his coronary arteries were not studied.[4]

Submitral aneurysms may be single or multiple and may extend, as here, superiorly to distort the left atrium or inferiorly into the ventricular wall or septum. They may communicate with the left ventricle via single or multiple communications and may contain thrombus. We know of no other case where thrombus within a submitral aneurysm has been discovered on echocardiography. Patients may present with emboli but the relatively narrow neck of the aneurysm makes this uncommon, unlike aneurysms associated with coronary artery disease.[5]

Most patients present, as here, in heart failure which may be acute or chronic. Mitral regurgitation is present in up to 68% of cases.[6] Apical systolic and diastolic murmurs caused by blood flow into and out of the aneurysm via its narrow neck and indistinguishable from those of mitral valve disease have been described. There was no turbulent flow within the aneurysm on colour flow Doppler mapping in our patient. Other patients may present with chest pain (attributed to either coronary artery compression or pericardial inflammation) or with an abnormal chest *x* ray.

The aneurysm is usually visible on a chest *x* ray, most commonly as a bulge on the left cardiac border. In this case a discrete shadow was noted at the right heart border with straightening of the left heart border, mimicking a large left atrium and doubtless contributing to the initial misdiagnosis of rheumatic mitral valve disease.

Cardiac angiography has been the mainstay of diagnosis although there have been two case reports in the past decade in which the diagnosis was made on the basis of cross sectional echocardiography and the two techniques must be regarded as complementary.[7 8] In neither case was thrombus present within the aneurysm.

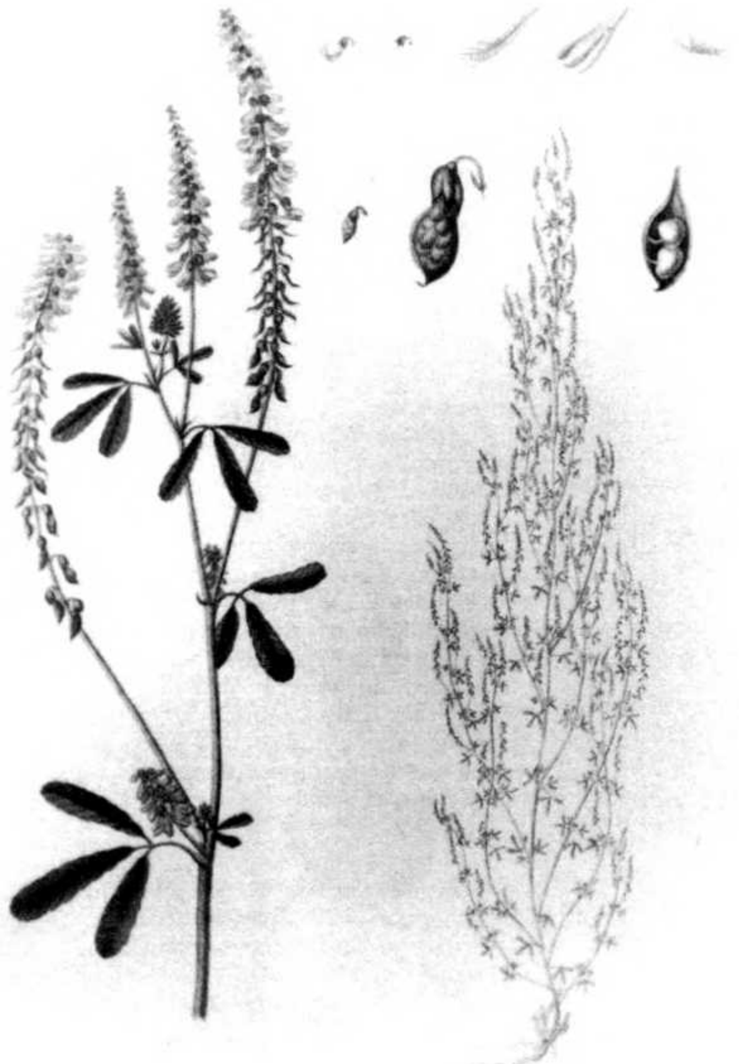
This condition is strongly associated with pulmonary tuberculosis.[9] It is unclear if the presence of a submitral aneurysm in some way predisposes patients to develop tuberculosis or if the association merely represents the high incidence of tuberculosis in patients from sub-Saharan Africa.

While symptom free patients have a good prognosis, those presenting in heart failure usually die within months. Sudden death has been recorded. Initial attempts at surgical excision were associated with a high mortality; however, the use of cardiopulmonary bypass and advances in technique have dramatically improved the safety of this procedure.[10]

This rare but important condition should be considered in patients of African origin in the clinical differential diagnosis of mitral valve disease and in the echocardiographic differential diagnosis of masses apparently within the left atrium.

1 Jacobs HD, Elliott GA. Cardiac ventricular aneurysm in South Africa. *Acta Med Scand suppl* 1955;**306**:84–95.
2 Abrahams DG, Barton CJ, Cockshott WP, Edington GM, Weaver EJM. Annular subvalvular left ventricular aneurysms. *Q J Med* 1962;**31**:345–60.
3 Lintermans JP. L'anverism ventriculaire gauche chez le jeune africain: a propos de 23 cas. *Arch Mal Coeur* 1972;**70**:129–34.
4 Pocock WA, Cockshott WP, Ball PJA, Steiner RE. Left ventricular aneurysms of uncertain aetiology. *Br Heart J* 1965;**27**:184–92.
5 Chesler E, Tucker RKB, Barlow JB. Subvalvular and apical left ventricular aneurysms in the Bantu as a source of systemic emboli. *Circulation* 1967;**35**:1156–62.
6 Kanarek KS, Bloom KR, Lakier JB, *et al*. Clinical aspects of submitral left ventricular aneurysms. *S Afr Med J* 1973;**47**:1225–9.
7 Davis MD, Caspi A, Lewis BS, *et al*. Two-dimensional echocardiographic features of sub-mitral left ventricular aneurysm. *Am Heart J* 1982;**103**:289–90.
8 Gupta SR, Gupta SK, Reddy KN, *et al*. Subvalvular aneurysm; two dimensional echocardiographic features. *Jpn Heart J* 1988;**29**:747–51.
9 Beheyt P, Joris H. L'anevrisme ventriculaire, d'origine tuberculeuse, chez le jeune africains: etude de 3 cas. *Acta Cardiol* 1963;**18**:113–42.
10 Antunes MJ. Submitral left ventricular aneurysms: correction by a new transatrial approach. *J Thorac Cardiovasc Surg* 1987;**94**:241–5.

PLANTS IN CARDIOLOGY



Melilotus officinalis (L.) Lam. *Flora Danicae* 1787: volume vi; plate 934.

Dicoumarol and warfarin

The poor soil, low rainfall, and hard winters of the North American prairies made it difficult to grow crops for animal feed until the melilots or sweet clovers, *Melilotus alba* and *M officinalis* (Leguminosae), were introduced from Europe early this century. They did well and were used for winter feed. In 1922 a new and mysterious disease of cattle was reported in Alberta by a veterinary surgeon F S Schofield who noted that cattle fed on mouldy sweet clover hay were dying of haemorrhage. Properly cured hay was harmless. Schofield found that the clotting time was prolonged: a few years later L M Roderick a veterinary surgeon in Dakota showed that this was due to a reduced crude prothrombin fraction in the blood. The coincidental introduction by Dr A J Quick of his one stage prothrombin method proved essential for further progress. Dr K P Link, who worked in Wisconsin where the disease was common, then took up the search for the enigmatic "haemorrhagic agent". It was six years before the agent was isolated in his laboratory by H A Campbell at dawn on 28 June 1939. It was shown to be a derivative of coumarin—the substance that gives a sweet smell to new mown hay—and was named bishydroxycoumarin. It is formed by fungal action in mouldy sweet clover by oxidation of coumarin to 4-hydroxycoumarin which is then coupled with formaldehyde. On 1 April 1940 it was synthesised. It was first used clinically as an oral anticogulant at the Mayo Clinic in 1941. The American trade name was dicumarol; and this was adapted in Britain to become the official name dicoumarol.

Link got tuberculosis in 1945 and, having unsuccessfully tried out dicumarol as a rat poison in 1942, he spent six months in the sanatorium reading about the history of rodent control. From 1946 to 1948 his laboratory staff reappraised the synthetic coumarin derivatives that they had made and found that number 42 had a potent and uniform anticoagulant action. Link proposed it as the ideal rodenticide and coined its name warfarin from the Wisconsin Alumni Research Foundation, which had promoted its use, plus the suffix from coumarin (*Circulation* 1959;**19**:97–107). Though dicumarol was enthusiastically used by clinicians warfarin, a rat poison, was ignored—until an army recruit failed to commit suicide after taking a huge dose. Warfarin was soon shown to be better and safer than dicumarol. It was introduced into clinical practice in 1954.

A HOLLMAN

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Intrapulmonary agenesis of venous system and bronchopulmonary arterial anastomosis

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Abstract

Agenesis of the intrapulmonary and extrapulmonary veins of the right lung was found by angiography and histological examination in a three year old boy. Blood supplied by the intersegmental arteries drained via the pulmonary arteries of the right lung into main and left pulmonary arteries. This caused a shunt between the aorta and pulmonary artery. Agenesis of the pulmonary venous system as a cause of left to right shunt has not been reported before.

Several forms of pulmonary venous abnormalities, such as pulmonary vein stenosis or atresia[1 2] and total or partially abnormal pulmonary venous connections[3] to various sites, have been described. However, the complete congenital absence or agenesis of intrapulmonary and extrapulmonary veins of one lung has not been reported before. There are 17 reports of a fistulous communication between the internal mammary or intercostal artery and the pulmonary artery[4–6]; but all of these cases had normal pulmonary venous return. We report a child with complete agenesis of the intrapulmonary and extrapulmonary veins of the right lung.

Case report

CLINICAL FEATURES

A three year old boy presented with a history of recurrent lung infections since birth. There were no other cardiovascular or respiratory symptoms. Growth and development were normal. The perinatal and family histories were unhelpful.

He had normal vital signs and no cyanosis. His height and weight were in the tenth percentile. Peripheral pulses were normal with a blood pressure of 100/50 mm Hg in the right arm. Cardiac findings included an apical impulse in the fourth left intercostal space inside the midclavicular line. No heave or thrill were present. On auscultation first and second heart sounds were normal. No systolic or diastolic heart murmurs were present. Examination of the chest showed decreased breath sounds over the right hemithorax. There was no hepatosplenomegaly. The rest of the physical examination was unremarkable.

Results of cardiac catheterisation

Site	*Saturations (%)*	*Pressures (mm Hg)*	*Mean (mm Hg)*
Superior vena cava	73		
Right atrium	66	a–7, v–5	4
Right ventricle	65	27/0–6	
Main pulmonary artery	86	23/12	18
Left pulmonary artery	80	22/12	18
Right pulmonary artery	96	24/11	18
Left ventricle	98	74/0–8	
Aorta	99	73/41	59

Assumed oxygen consumption = 140 ml/min; cardiac index = 3 4 l/min/m^2; pulmonary index = 5·9 l/min/m^2; QP·QS = 1·7:1; pulmonary vascular resistance (RP) = 3 0 Wood units; systemic vascular resistance (RS) = 17·6 Wood units, RP:RS = 0:17.

INVESTIGATIONS

A complete blood count with differential count, sedimentation rate, urine analysis, hepatic and renal profiles, serum γ globulins, tuberculin skin test, and sweat chloride test were negative. Multiple blood and sputum cultures were sterile. The arterial blood gas profile while he was breathing room air showed pH 7·38, Paco$_2$ 37, and Pao$_2$ 87 mm Hg.

Chest x ray

The trachea and mediastinum were shifted to the right side. The right hemidiaphragm was raised. There were diffuse infiltrates and pleural thickening in the right lung. Bronchography showed absence of the posterior segment (RB2) of the right upper lobe. The right middle lobe was normal. Except for the basilar segment (RB9), the other segmental bronchi of the right lower lobe were clustered together and were much smaller in diameter and length than normal. A ventilation and perfusion lung scan showed decreased ventilation and no perfusion of the right lung. The left side was normal.

Electrocardiogram

There was left axis deviation but the electrocardiogram was otherwise normal for age. Cross sectional echocardiography with Doppler studies showed a reverse flow pattern in the right pulmonary artery and a normal cardiac anatomy.

Cardiac catheterisation

The pressures in the right and left sides of the heart were normal (table). There was a step-up in oxygen saturation in the main and left pulmonary arteries. The oxygen saturation in the right pulmonary artery was 99%. The calculated QP:QS was 1·7:1 (assumed oxygen consumption 140 ml/min). Systemic and pulmonary resistances were normal.

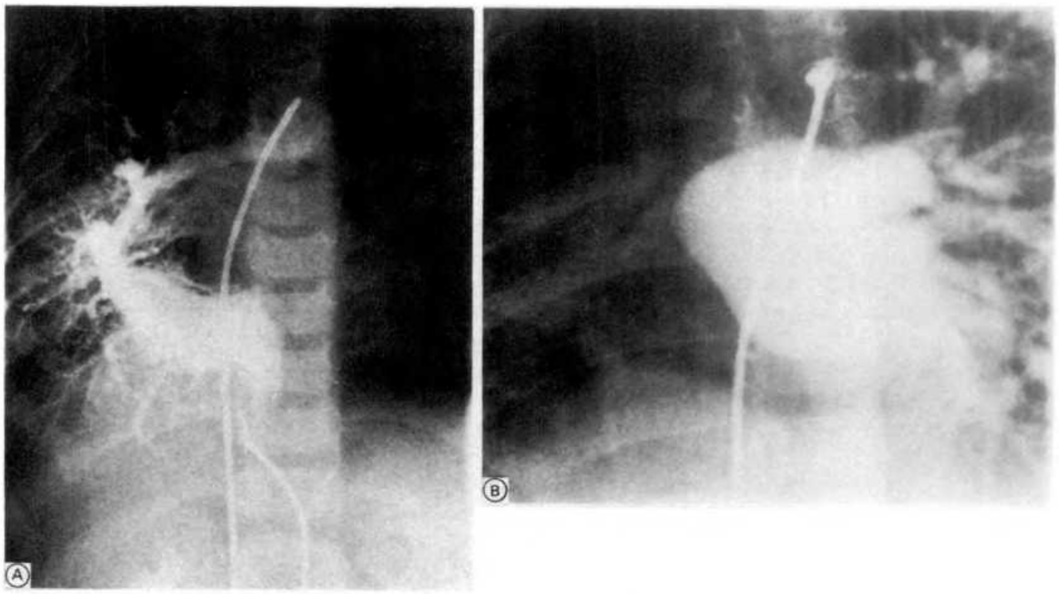

Figure 1 Venous phase of arterial angiograms. (A) Dye was injected into the systemic artery supplying the right lung. This showed the capillary phase and retrograde filling of the pulmonary arterial tree. Dye flowed retrogradely from the right to the left pulmonary artery. (B) Dye was injected into the main pulmonary artery. During laevophase the left pulmonary veins were seen entering the left atrium. No pulmonary veins were seen on the right side.

Cineangiography

The main pulmonary artery angiogram showed that there was a continuous flow of unopacified blood from the peripheral to the central right pulmonary artery and then into the main and left pulmonary arteries. Dye selectively injected into the distal portion of the right pulmonary artery was washed back via the central right pulmonary artery into the main and left pulmonary arteries. There was no forward flow into the capillaries and veins of the right lung. The left lung was normal. An aortic angiogram showed that systemic arteries, two from the thoracic aorta and one from the abdominal aorta, supplied the right lung. The selective angiograms from these arteries showed the flow into the capillary bed of the right lung. During the laevophase of these angiograms (fig 1) dye collected into the pulmonary arterial tree and then left the lung via the right pulmonary artery into the main and left pulmonary arteries. Neither right pulmonary nor systemic arterial injections showed a venous system from the right lung.

Surgery

Right pneumonectomy was performed. Three systemic vessels were identified: two arising from the thoracic aorta entered the hilar region and one from the abdominal aorta entered through the diaphragm into the base of the lung. No pulmonary veins, fibrous strands, or cord connected the right lung to the left atrium.

HISTOLOGY

We examined serial sections made of tissue at various levels of the formalin fixed, uninflated right lung. Systemic elastic arteries entered the right lung, two in the hilar region and one on the diaphragmatic surface of the lung. These vessels ended in a plexus of capillaries close to the airways and acini. The pulmonary arteries also anastomosed with this plexus. The muscular pulmonary arteries, predominantly in the lower lobe, showed changes—Heath and Edwards classification types I and II. An occasional artery showed plexiform lesions and venous-like dilatations. There was

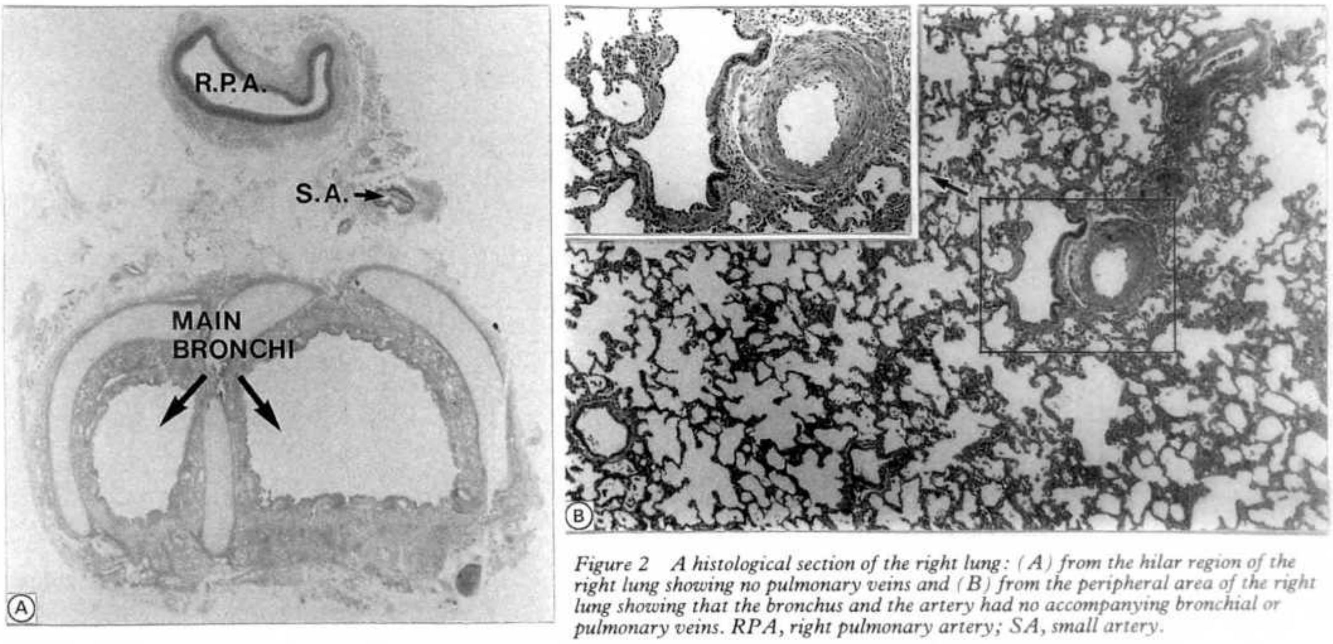

Figure 2 A histological section of the right lung: (A) from the hilar region of the right lung showing no pulmonary veins and (B) from the peripheral area of the right lung showing that the bronchus and the artery had no accompanying bronchial or pulmonary veins. RPA, right pulmonary artery; SA, small artery.

no right pulmonary vein. We found no pulmonary or bronchial veins accompanying the pulmonary arteries and airways (fig 2). The airways and acini seemed to be normal except for occasional foci of early emphysematous lesions. We also found irregularly distributed, mild septal, interstitial, and pleural fibrosis.

Discussion

There are 17 case reports of systemic to pulmonary artery anastomosis; in most a right internal mammary to pulmonary artery fistula affected either a lobe or a segment of a lobe.[4-6] These fistulas were mostly congenital. However, systemic to pulmonary artery fistulas secondary to trauma,[6-8] inflammation,[9] or neoplasms[10] have also been described. However, in all these patients, venous drainage of the affected lobe was normal; whereas in our patient we found neither an intrapulmonary nor extrapulmonary venous system of the right lung by angiography or histology.

The venous system of the lungs develops from two different sources.[11] Initially, the splanchnic plexus arising from the foregut provides the venous drainage into the systemic veins for the developing pulmonary capillaries. Later, with the development of the common pulmonary vein and absorption of the systemic venous connection, pulmonary venous drainage is established into the left atrium. We speculate that in early stages of development the failure of the splanchnic system to connect with the developing pulmonary capillaries of the right lung mesenchyma resulted in the persistence of the anastomosis between the intersegmental and pulmonary arteries. Postnatally this anastomosis led to a systemic to pulmonary artery shunt. The absence of pulmonary veins in the lung has not been reported before.

Non-invasive investigations in this child did not show the true nature of the abnormality, whereas cineangiography and cardiac catheterisation did. We recommend cineangiography and cardiac catheterisation in patients with suspected pulmonary vascular malformations.

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1 Lucas RV, Woolfrey BF, Anderson RC, Lester RG, Edwards JE. Atresia of the common pulmonary vein *Pediatrics* 1962.729–39.
2 Bini RM, Cleveland DC, Celeallos R, *et al* Congenital pulmonary vein stenosis *Am J Cardiol* 1984;54 369–75.
3 Kingston HM, Patel RG, Watson GH Unilateral absence or extreme hypoplasia of pulmonary veins *Br Heart J* 1983;49 148–53
4 Hirsch M, Maroko I, Gueron M, Goleman L. Systemic-pulmonary arteriovenous fistula of traumatic origin· a case report. *Cardiovasc Intervent Radiol* 1983,6·160–3
5 Izumi S, Okamoto M, Beppu S, *et al* Intercostal artery to pulmonary artery fistula *Am J Cardiol* 1984,54:688–9.
6 Fein KB, Godwin JD, Moore AV, Moran JF, Young WG Systemic artery-to-pulmonary vascular shunt· a complication of closed-tube thoracostomy. *Am J Radiol* 1984;140 917–9
7 Cox PA, Keshishian JM, Blades BB. Traumatic arteriovenous fistula of the chest wall and lung secondary to insertion of an intercostal catheter. *J Thorac Cardiovasc Surg* 1967;54·109–12
8 Saito T, Matsuda M, Yamaguchi T, Matsuzaki T, Nagakawa S, Akatsuka N. A case of traumatic systemic-pulmonary arteriovenous fistula *Jpn Heart J* 1975;16·196–203
9 Ishikawa T Systemic artery-pulmonary artery communication in Takayasu's arteritis. *Am J Roentgenol* 1977, 128.389–93.
10 Dunn RP, Wexler L. Systemic-to-pulmonary fistula in intrapulmonary Hodgkin's disease *Chest* 1972;66 590–4
11 Spencer H. *Pathology of the lung* 4th ed. New York: Pergamon Press, 1985:13–16

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WORKING PARTY REPORT

Recommendations for pacemaker prescription for symptomatic bradycardia

Report of a working party of the British Pacing and Electrophysiology Group

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After the first permanent pacemaker implantation in 1958,[1] the initial developments in pacemaker technology were aimed towards more efficient pacemaker performance. The standard mode of pacing in these early years was single chamber ventricular stimulation and this became established as effective lifesaving therapy.[2] Over the past 10 years, however, there has been a wealth of different features incorporated into pacemaker design, including programmability, telemetry, and different "modes" of pacing.[3-6]

The British Pacing and Electrophysiology Group (BPEG) was formed as a specialist subgroup of the British Cardiac Society in 1976 and consists of cardiologists, technicians, and representatives from the pacemaker manufacturing industry. BPEG is organised for the purposes of scientific communication, research, and education specifically related to cardiac pacing and electrophysiology. The group organises an active scientific and educational programme and has more than 200 members.

A working party was formed by BPEG to establish guidelines for the use of the different modes of cardiac pacing. The nomenclature for pacemaker modes accepted for international use is that produced by a combined working party of the North American Society of Pacing and Electrophysiology (NASPE) and the British Pacing and Electrophysiology Group (BPEG) known as the NBG (NASPE/BPEG generic) code.[7] This is a code of five letters of which the first three are most often used (table 1). In addition, a fourth letter R is used if adaptive rate pacing is programmed. In adaptive rate (or rate responsive) pacing there is an additional sensor in the pacemaker system that detects a physiological or semi-physiological result of exercise or emotion and increases the pacemaker rate on the basis of a programmable algorithm. Sensors that are presently successfully used in pacemakers include activity,[8] respiratory rate[9] and minute ventilation,[10] right ventricular pressure (dP/dt),[11] central venous temperature,[12] evoked QT interval,[5] and oxygen saturation.[13] Whatever the sensor effective adaptive rate pacing can be used independently of atrial activity. Recently, activity sensing has been combined with dual chamber pacing.[6]

The NBG code also uses a fifth letter relating to antitachycardia function which is not discussed in this document. Each of the pacing modes under discussion is described in the Appendix.

Table 1 NBG pacemaker code

FIRST letter signifies the chamber(s) of the heart being PACED	
A	(atrium)
V	(ventricle)
D	(atrium and ventricle)
SECOND letter indicates the chamber(s) being SENSED	
A	(atrium)
V	(ventricle)
D	(atrium and ventricle)
THIRD letter indicates the MODE of sensing	
I	(inhibited)
T	(triggered)
D	(inhibited and triggered)

AHA/ACC Guidelines

Over the past 30 years the clinical indications for pacing have increased to include a large number of different cardiac arrhythmias. To clarify the situation a combined working group of the American Heart Association and the American College of Cardiology has published guidelines on the indications for pacing.[14] There are three main classes of patients, which may be summarised as follows:

Class I—Conditions in which there is general agreement that permanent pacemakers should be implanted. This includes syncopal patients with complete heart block or prolonged sinus arrest.

Class II—Conditions in which permanent pacemakers are frequently used but there is some divergence of opinion about whether they are needed. Included within this group are the sick sinus syndrome patients without syncope but with other symptoms and also patients with symptomatic incomplete atrioventricular block. Asymptomatic complete heart block is also in this category.

Class III—Conditions in which there is general agreement that pacemakers are not necessary. This includes asymptomatic patients with sinus node disease or first or second degree atrioventricular block and patients with unexplained syncope without obvious cardiac arrhythmia.

BPEG Guidelines

The AHA/ACC recommendations have

provided a logical foundation to guide physicians considering cardiac pacing as a treatment for their patients. There are, however, some areas where published data indicate that pacing should be more widely used as a first-line therapy.

Carotid sinus syndrome[15] and, more recently, malignant vasovagal syncope[16] would now qualify as firm indications for pacemaker implantation when appropriate investigation shows a major cardioinhibitory effect.[16 17] Furthermore, untreated persistent second degree atrioventricular block, even in asymptomatic patients, has been shown to be associated with a reduced expectation of life. In this group of patients prophylactic pacing restores life expectation to normal.[18] The Wenckebach phenomenon can occur during sleep in normal individuals with high vagal tone and these people do not need to be considered for treatment. However, those asymptomatic patients with either Wenckebach or Mobitz II second degree atrioventricular block occurring during much of the day and night would qualify for pacemaker implantation,[19] as would patients with asymptomatic complete heart block. With these modifications, the AHA/ACC guidelines can be used both as a clinical aid and a basis for medical audit of the indications for pacemaker implantation. However, recommendations about the choice of pacemaker prescription are limited.

Choice of pacemaker mode

When the choice of pacemaker mode for an individual patient is considered, the ideal is production of a paced cardiac rhythm with as many features of normal sinus rhythm as possible (table 2). The guidelines proposed in this paper are based on an attempt to allow the pacemaker response to behave as physiologically as possible. This includes restoration of atrioventricular synchrony and/or rate adaptive pacing wherever needed. To achieve this ideal, detailed information of the underlying cardiac rhythm should be obtained before or during pacemaker implantation. The following features should be considered.

ATRIOVENTRICULAR SYNCHRONY

Pacemaker systems that maintain atrioventricular synchrony with a physiological atrioventricular interval have been shown to increase cardiac output both at rest and on exercise in patients with normal and impaired left ventricular function.[20] Even in the absence of an exercise induced rate response, atrioventricular synchrony reduces the number of minor symptoms (dizziness, lethargy) that are associated particularly with sinus node disease.[21]

Table 2 General principles of pacemaker choice

(1) The ventricle should be paced if there is actual or threatened atrioventricular block.
(2) The atrium should be paced/sensed unless contraindicated.
(3) Rate response is not essential if the patient is inactive or has a normal chronotropic response.
(4) Rate hysteresis may be valuable if the bradycardia is intermittent.

RATE MODULATION

Adaptive rate (or rate responsive) pacing significantly increases cardiac output on exercise in patients with atrioventricular block[8] and sinus node disease.[22] Patients treated with rate responsive pacemakers achieve higher workloads and greater exercise tolerances.[8 22]

ATRIAL PACING

Evidence is accumulating of a considerable reduction in the high spontaneous incidence of the development of atrial fibrillation[23] and of systemic emboli[24 25] in patients with sinus node disease treated by a pacing system that maintains atrioventricular synchrony.

LEFT VENTRICULAR PERFORMANCE

Spontaneous (normal) ventricular contraction may allow better ventricular function than a paced ventricular beat.[26] Typically, the ventricular pacing lead is inserted into the right ventricle and delivery of the pacing stimulus at this site results in the equivalent of left bundle branch block. This causes measurable impairment of left ventricular contraction which may be of haemodynamic relevance in both normal[27] and compromised left ventricles.[28]

RATE HYSTERESIS

Hysteresis is a programmed feature whereby the pacemaker paces at a faster rate than the sensing rate. For example, pacing at 80 pulses a minute with a hysteresis rate of 55 means that the pacemaker will be inhibited at all rates down to 55 beats per minute. Having been activated at a rate below 55, the pacemaker then switches on and paces at 80 pulses a minute. Unless careful record is made in the patient's notes that hysteresis has been programmed, pacemaker malfunction could be incorrectly inferred.

ATRIAL ARRHYTHMIAS

The presence of atrial activity other than chronic or frequently repetitive atrial flutter or fibrillation generally requires an atrial pacemaker electrode. Paroxysmal atrial arrhythmias are not a contraindication to atrial pacing[29] or sensing in most cases, because atrial pacing may stabilise the atrial rhythm[30]; in others concomitant drug treatment may be beneficial. In those patients with atrial bradycardia and intact atrioventricular conduction, a single chamber atrial pacemaker can be considered to be the treatment of choice.[29] However, the presence of minor abnormalities of atrioventricular conduction—for example first degree atrioventricular block (PR interval prolongation) or bundle branch disease with normal atrioventricular conduction generally suggests a need for placement of a ventricular lead in patients with symptomatic sinoatrial disorders.[31 32]

TYPES OF ARRHYTHMIAS REQUIRING PACING

Table 3 shows the percentage occurrence of arrhythmias in a typical population of patients with bradycardia requiring pacing.[33] For the purposes of table 3, sinus node disease includes

Table 3 Percentage incidence of various bradyarrhythmias in a typical pacemaker population

Arrhythmia	%
Sinus node disease	25
AV block	42
Sinus node disease + AV block	10
Atrial fibrillation + AV block	13
Carotid and vasovagal syndromes	10

AV, atrioventricular

sinus bradycardia, sinus arrest, sinoatrial block, and the tachycardia-bradycardia syndome, but does not include atrial bradyarrhythmias associated with carotid sinus syndrome or malignant vasovagal syndrome.

CAROTID SINUS AND MALIGNANT VASOVAGAL SYNDROMES

Carotid sinus syndrome can be diagnosed in a patient with syncope by the presence of a positive carotid sinus massage test. The development of either a period of asystole in excess of three seconds, or the appearance of atrioventricular block, during five to six seconds of firm carotid sinus massage (not compression) is regarded as diagnostic.[17] The test should not be performed in patients with carotid artery bruits or documented stenosis, after recent myocardial infarction, or if the patient is digitalised. Variations of carotid sinus syndrome include micturition syncope,[34] cough syncope,[35] and deglutition syncope.[36] Malignant vasovagal syncope can be demonstrated by performing a 60° head-up tilt test. Syncope associated with bradycardia or hypotension or both occurs within 40 minutes.[16]

In patients with carotid sinus and malignant vasovagal syndromes there are two components to the syncope—bradycardia (cardioinhibition) and peripheral and splanchnic vasodilation (vasodepression). In patients with a pronounced vasodepressor effect, pacing is less successful than in patients with a dominant cardioinhibitory effect.[15] If patients are suitable for pacing the mode of choice for carotid sinus syndrome and malignant vasovagal syndrome is DDI,[37] frequently with hysteresis as an added feature.[38]

Table 4 Recommended pacemaker modes

Diagnosis	*Optimal*	*Alternative*	*Inappropriate*
SND	AAIR	AAI	VVI VDD
AVB	DDD	VDD	AAI DDI
SND and AVB	DDDR DDIR	DDD DDI	AAI VVI
Chronic AF with AVB	VVIR	VVI	AAI DDD VDD
CSS	DDI	DDD VVI*	AAI VDD
MVVS	DDI	DDD	AAI VVI† VDD

The optimal mode of pacing should be considered for most patients. The alternative mode should be regarded as being less satisfactory, but acceptable in some groups of patients—for example those who are disabled by another disease, those with very intermittent symptoms, or those who have a short life expectancy because of another disease. When a patient with, for example, a previous hemiplegia or with terminal neoplasia has atrioventricular block, VVI may suffice to reduce symptoms.

*If VVI is ever chosen for the management of carotid sinus syndrome rate hysteresis is recommended [38] Patient selection should follow the guidelines suggested by Brignole *et al*.[39]

†See reference.[40]

AVB, atrioventricular block; AF, atrial fibrillation or flutter, MVVS, malignant vasovagal syndrome, SND, sinoatrial node disease; CSS, carotid sinus syndrome.

ATRIAL TRACKING PACING SYSTEMS

It is recognised that the pacing system known universally as DDD behaves for most of the time as a VDD system. The only difference is the behaviour at the lower programmed rate, where the DDD paces into the atrium and the VDD has a back-up VVI mode. For the patient with bradycardia that is slower than the lower programmed rate, this may have significant disadvantages including pacemaker syndrome. In sinus node disease the potential benefit of pacing the atria is not available in VDD mode.

Table 4 shows the recommended modes, based on these principles, for patients with all varieties of bradyarrhythmias requiring pacing.

Complications of inappropriate mode selection

Inappropriate pacemaker modes (table 4) should be avoided to prevent the following complications:

(*a*) Pacemaker syndrome,[41] which is caused either by retrograde conduction from the ventricle to the atrium or by lack of synchronous atrioventricular activity that results in loss of atrial transport function. Pacemaker syndrome may cause symptoms of syncope or pre-syncope as a result of retrograde conduction.[41] Dyspnoea may occur where there is high pulmonary venous pressure and low cardiac output and associated mitral regurgitation (demonstrable by Doppler echocardiography) caused by a lack of atrioventricular synchrony.[42] Neck pulsation may be seen when retrograde atrioventricular conduction causes tricuspid regurgitation or right atrial contraction against a closed tricuspid valve. The true incidence of pacemaker syndrome is not well defined but it is thought that 10% of patients paced VVI have quite severe symptoms and another 15% have a reduced quality of life as a result.[41] All these symptoms can be relieved by a more appropriate pacing mode.

(*b*) Inappropriate atrial tracking of atrial tachyarrhythmias by a DDD or VDD system.[43] Atrial tachycardia, flutter, or fibrillation produce an electrogram which can be easily detected by the atrial sensing amplifier of the pacemaker, which will then track this rhythm at its upper pacing rate. Newer dual chamber rate adaptive systems incorporate algorithms that prevent or minimise inappropriate ventricular pacing in response to atrial fibrillation.

(*c*) Additional atrioventricular block in a patient with sinus node dysfunction may not be easily detected initially.[44] Normal 1:1 atrioventricular conduction at atrial pacing at rates of 140 usually indicates adequate atrioventricular nodal function. The appearance of the atrioventricular Wenckebach block at slower rates may be considered indicative of important impairment of atrioventricular node conduction which warrants placement of a ventricular lead. There may be other evidence of inadequate atrioventricular conduction from Holter monitoring, exercise stress testing, or His bundle electrography.

(*d*) Lack of physiological heart rate response on exercise. Unrecognised sinus node dysfunction in a patient with atrioventricular block would result in inadequate performance of an atrial tracking (DDD) pacemaker. In addition, there are some patients with sinus node disease treated by atrial rate modulated pacing systems who may develop abnormal atrioventricular conduction on exercise[45] resulting in an unusual variety of pacemaker syndrome.

Additional guidelines

The following additional guidelines are recommended to enable accurate assessment of a patient requiring pacemaker implantation:

(*a*) In selected patients atrioventricular conduction should be assessed by Holter, carotid sinus massage, and atrial pacing to assess the atrioventricular Wenckebach point at the time of implant if atrial pacing (AAI) is being considered.

(*b*) Retrograde atrioventricular conduction should be assessed by ventricular pacing if VVI or VVIR pacing is considered. Head-up tilting during ventricular pacing may reveal latent symptoms.

(*c*) If VDD or DDD pacing is being considered in active patients the chronotropic response of the sinus node should be assessed by Holter or exercise testing. If the response is inadequate an appropriate sensor driven system may be needed.

Consequences of increased use of dual chamber and rate responsive pacing

COST

A VVIR unit costs about 40–50% more and a dual chamber unit costs 40–100% more than a multiprogrammable single chamber pacemaker. In addition, a dual chamber system requires two pacing leads which further increase the cost. Rate-responsive pacing systems have a shorter battery lifetime than non-rate responsive modes because of their overall faster pacing rate and the inherent current drain of the sensor.

However, pacing is cost effective in terms of relief of symptoms, prolongation of life, and improvement of the quality of life.[20 46–50] Patients with pacemakers rarely need to be readmitted to hospital because of problems. So a tailored pacemaker prescription that follows the guidelines in this report will offer good value for money.

FOLLOW UP

Patient follow up with VVIR and dual chamber systems is initially more complex and time consuming. Additional programming is necessary together with Holter taping and exercise testing where required. Support staff need to be trained. When the pacing system has been "fine tuned" to the individual patient's requirements, however, subsequent follow up is less time consuming.

COMPLICATIONS

Complex pacing systems are more susceptible to problems. Dual chamber systems require two endocardial leads and lead related complications are therefore slightly increased.[51] Inappropriate programming may also give rise to difficulties. A badly programmed sensor may give excessive or inadequate rate responses. It is possible to select an inappropriate sensor system for an individual patient—for example, an activity sensor in a bedbound patient or a minute-ventilation sensor in a patient with chronic lung disease are as inappropriate as a DDD system would be in a patient with atrial flutter.

Which hospitals should implant and follow up pacemakers?

Over recent years, it has been the policy of some regional health authorities to encourage pacemaker implantation in district general hospitals. This is acceptable but it demands at least one cardiologist fully trained in the complex disciplines of dual chamber pacing and follow up, together with at least one similarly trained physiological measurement technician. Hospitals with only one cardiologist would need to make arrangements with similarly trained staff in a neighbouring district to cover periods of absence.

Choice of pacing system

When choosing a pacemaker system for a patient, a physician usually adopts one of three policies:

(*a*) A basic VVI system for everyone, irrespective of need, symptoms, or electrocardiographic findings. This policy is clearly inappropriate.

(*b*) The routine use of the most sophisticated dual chamber rate adaptive pacemaker (DDDR) for every patient, programmed to match the patients' needs. This is medically acceptable, but inappropriate on grounds of cost.

(*c*) A device that is carefully prescribed according to the guidelines in this report. This again is medically sound, but this policy requires thorough assessment of the patient before pacemaker implantation and meticulous follow up.

This working party of BPEG recommends that selection of the appropriate pacemaker mode should follow the basic principles and guidelines discussed above. This will require a fairly radical change of practice in some pacemaker centres in the United Kingdom and additional funding for the more complex pacemaker systems and their subsequent follow up.

1 Elmqvist R, Senning A An implantable pacemaker for the heart. Smyth CN, ed In. *Medical electronics. Proceedings of the second international conference on medical electronics* London: Illife, 1959:253.
2 Ginks W, Leatham A, Siddons H. Prognosis of patients paced for chronic atrioventricular block. *Br Heart J* 1979;41.633–6
3 Sutton R, Citron P, Perrins J. Physiological cardiac pacing. *PACE* 1980;3:207–17.

4 Clarke M, Allen A. Use of telemetered electrograms in the assessment of normal pacemaker function. *J Electrophysiol* 1987;1:388–95

5 Rickards AF, Norman J. Relation between QT interval and heart rate. New design of a physiologically adaptive cardiac pacemaker. *Br Heart J* 1981;45·56–61.

6 Kappenberger L, Hepers L. Rate responsive dual chamber pacing. *PACE* 1986,9:987–91

7 Bernstein A, Camm J, Fletcher R, *et al* The NASPE/BPEG generic pacing code for antibradyarrhythmia and adaptive rate pacing and antitachycardia devices. *PACE* 1987, 10:794–9.

8 Humen D, Anderson K, Brumwell D, Huntley S, Klein G. A pacemaker which automatically increases its rate with physical activity In: Steinbach K, Glogard A, Laszkovicsa D, Schneibelhofer W, Weber H, eds. *Cardiac pacing* Darmstadt: Steinkopff Verlag, 1983.252–64.

9 Rossi P, Plicchi G, Canducci G, Rognoni G, Aina F. Respiration as a reliable physiological sensor for controlling cardiac pacing rate. *Br Heart J* 1984;51:7–14.

10 Lau C, Antoniou A, Ward D, Camm AJ. Reliability of minute ventilation as a parameter for rate responsive pacing. *PACE* 1989;12:321–30.

11 Sutton R, Sharma A, Ingram A, Camm J, Lindemans F, Bennett T. First derivative of right ventricular pressure as a sensor for an implantable rate responsive VVI pacemaker [abstract]. *PACE* 1988;11.487.

12 Alt E, Volker R, Hogl B, MacCarter D. First clinical results with a new temperature-controlled rate responsive pacemaker. *Circulation* 1988;78 (suppl III):116–24

13 Stangl K, Wirtzfeld A, Heinze R, Laule M. First clinical experience with an oxygen saturation controlled pacemaker in man. *PACE* 1988,11 1882–7.

14 Frye RL, Collins JJ, DeSanctis RW, *et al.* Guidelines for permanant pacemaker implantation—May 1984 A report of the joint American College of Cardiology/American Heart Association Task Force on assessment of Cardiovascular Procedures (Subcommittee on Pacemaker Implantation) *J Am Coll Cardiol* 1984;4.434–42.

15 Morley CA, Perrins EJ, Grant P, Chan SL, McBrien DJ, Sutton R. Carotid sinus syncope treated by pacing. Analysis of persistent symptoms and role of atrioventricular sequential pacing. *Br Heart J* 1982,47 411–8.

16 Fitzpatrick A, Sutton R Tilting towards a diagnosis in recurrent unexplained syncope *Lancet* 1988;i·658–60.

17 Morley C, Sutton R. Carotid sinus syndrome—editorial review. *Int J Cardiol* 1984;6:287–93

18 Shaw D, Kekwick C, Veale D, Gowers J, Whistance T. Survival in second degree atrioventricular block. *Br Heart J* 1985;53.587–93.

19 Campbell RWF. Chronic Mobitz type I second degree atrioventicular block. Has its importance been underestimated? *Br Heart J* 1985,53:585–6.

20 Kruse I, Arnman K, Conradson T, Ryden L. A comparison of the acute and long-term haemodynamic effects of ventricular inhibited and atrial synchronous ventricular inhibited pacing. *Circulation* 1981,65:846–55

21 Mitsuoka T, Kenny RA, Yeung TA, Chan SL, Perrins JE, Sutton R Benefits of dual chamber pacing in sick sinus syndrome. *Br Heart J* 1988,60:338–47.

22 Rognoni G, Bolognese L, Aina F, Occhetta E, Magnani A, Rossi P. Respiratory dependant atrial pacing, management of sinus node disease. *PACE* 1988;11:1853–9

23 Rosenqvist M, Brandt J, Schuller H. Long-term pacing in sinus node disease; effects of stimulation mode on cardiovascular morbidity and mortality. *Am Heart J* 1988;116·16–22.

24 Santini M, Alexidou G, Porto M, Santini A, Ammirati F, Ansalone G. The sick sinus syndrome. prognosis as function of age, conduction defects and pacing mode [abstract]. *PACE* 1989,12:1237.

25 Bianconi L, Boccadamo R, Di Florio A, *et al* Atrial versus ventricular stimulation in sick sinus syndrome; effects on morbidity and mortality [abstract] *PACE* 1989;12:1236

26 Theodorakis G, Fitzpatrick A, Ahmed R, Travill C, Sutton R. Doppler estimation of cardiac output during AAI and DDD pacing (with varying AV delay) at different pacing rates [abstract]. *PACE* 1989;12:1185.

27 DeNardo D, Antolini M, Pitucco O, *et al.* Effects of left bundle branch block on left ventricular function in apparently normal subjects. *Cardiology* 1988,75 365–71.

28 Gibson DG, Chamberlain DA, Coltart DJ, Mercer J. Effect of changes in ventricular activation on cardiac haemodynamics in man. Comparison of right ventricular, left ventricular, and simultaneous pacing of both ventricles *Br Heart J* 1971;33.397–400

29 Ryden L Atrial inhibited pacing—an underused mode of cardiac stimulation. *PACE* 1988;11·1375–9

30 Egobasti A, Gueunoun M, Sasdjian A, *et al.* Long-term follow-up of patients treated with VVI pacing and sequential pacing with special reference to VA retrograde conduction. *PACE* 1988,11 1929–34.

31 Sutton R, Kenny R. Natural history of sick sinus syndrome *PACE* 1986,9.1110–4.

32 Rosenqvist M, Obel I Atrial pacing and the risk for AV block: Is there a time for change of attitude? *PACE* 1989;12:97–101.

33 British Pacing and Electrophysiology Group Database—statistics for the City General Hospital, Stoke-on-Trent, 1986–1989.

34 Haldane JH. Micturition syncope *Can Med Assoc J* 1969, 101:712–4.

35 Hart G, Oldershaw P, Cull R, Humphrey P, Ward D Syncope caused by cough-induced complete atrioventricular block. *PACE* 1982;5 564–66

36 Igaluer S, Swartz B Heart block periodically induced by the swallowing of food in a patient with cardiospasm (vasovagal syncope). *Ann Otol Rhinol Laryngol* 1936; 45·875–81.

37 Sutton R, Ingram A, Clarke M. DDI pacing in the treatment of sick sinus, carotid sinus and vasovagal syndromes [abstract]. *PACE* 1988;11·827

38 Morley C, Perrins EJ, Chan SL, Sutton R. The role of rate hysteresis pacing in the hypersensitive carotid sinus syndrome. *PACE* 1983;6:1224–8

39 Brignole M, Menozzi C, Lolli G, Oddone D, Roti S. When is DDD pacing necessary and when is VVI pacing sufficient in carotid sinus syndrome? [abstract]. *PACE* 1989, 12:1169.

40 Fitzpatrick AP, Travill CM, Vardas PE, *et al.* Recurrent symptoms after ventricular pacing in unexplained syncope. *PACE* 1990;13:619–24.

41 Ausubel K, Furman S. The pacemaker syndrome *Ann Intern Med* 1985;103 420–9.

42 Naito M, Dreyfus L, David D, Nicholson E, Mardela T, Kmetzo J Re-evaluation of the role of atrial systole in cardiac hemodynamics: evidence for pulmonary venous regurgitation during abnormal atrioventricular sequencing. *Am Heart J* 1983;105.295–302.

43 Castellanos A, Lemberg L, Rodriquez-Tocker L, *et al* Atrial synchronised pacemaker arrhythmias, revisited *Am Heart J* 1968;76:199–205.

44 Steinbach K, Forohner K, Meisl F, *et al* Atrial stimulation In Pérez Gómez F, ed. *Cardiac pacing* Madrid. Grouz, 1985.629.

45 Clarke M, Allen A Rate responsive atrial pacing resulting in pacemaker syndrome [abstract] *PACE* 1987;10.1209.

46 Perrins JE, Morley CA, Chan SL, Sutton R Randomised controlled trial of physiological and ventricular pacing *Br Heart J* 1983;50 112–7

47 Lau CP, Rushby J, Leigh-Jones M, *et al* A double blind cross-over study on the symptomatology and quality of life in patients with rate responsive pacemakers [abstract]. *J Am Coll Cardiol* 1989;13 113.

48 Fitzgerald WR, Graham IM, Cole T, Evans DW Age, sex, and ischaemic heart disease as prognostic indicators in long-term cardiac pacing. *Br Heart J* 1979,42 57–60

49 Edhag O, Swann A. Prognosis of patients with complete heart block or arrhythmic syncope who were not treated by cardiac pacemakers. *Acta Med Scand* 1976,200.457–63

50 Williams A. Economics of coronary artery bypass grafting *BMJ* 1985;291 326–9.

51 Sutton R, Ingram A, Briers L, *et al.* Ten years of physiological cardiac pacing In· Belhassen B, Feldman S, Copperman Y, eds. *Cardiac pacing and electrophysiology.* Jerusalem: R & L Creative Communications, 1987 141–2

52 Cunningham T. Pacemaker syndrome due to retrograde conduction in DDI pacemaker. *Am Heart J* 1988; 115 478–9.

53 Ricci D, Rider A, Mason J Recurrent tachyarrhythmia associated with a bifocal demand pacemaker. *Chest* 1977, 72:120–3.

54 Den Dulk K, Lindemans FW, Banf W, *et al.* Pacemaker related tachycardia. *PACE* 1982,5 476–85

55 Torresani J, Egobasti A, Allard-Latour G. Pacemaker syndrome with DDD pacing *PACE* 1984,7 1148–51.

Appendix

Summary of commonly used pacemaker modes

AAI—Single chamber atrial pacing

Indications: —Sinoatrial node disease without atrioventricular block and without failure to increase rate on exercise.

Contraindications: —Atrioventricular block

—Persistent atrial tachyarrhythmias.

—Carotid sinus and vasovagal syndromes.

—Sinoatrial node disease with failure to increase rate on exercise.

Advantages: —Simple system using standard single atrial lead and standard multiprogrammable single chamber pacemaker.

—Atrioventricular synchrony maintained.

Disadvantages: —No rate response on exercise.

—No protection against atrioventricular block.

AAIR—Single chamber atrial pacing with rate response

Indications: —Sinoatrial node disease without atrioventricular block with failure to increase rate on exercise

Contraindications: —As for AAI mode

Advantages —Single atrial lead with standard pacemaker programmed to AAI mode with an additional rate adaptive sensor.

—Atrioventricular synchrony maintained.

Disadvantages: —No protection against atrioventricular block.

—Atrioventricular block not present at rest may develop at faster pacing rates due to mismatch between sensor determined pacing rate and autonomic nervous system influences on the atrioventricular node.

—Inappropriately long atrioventricular conduction times on exercise may result in pacemaker syndrome.[51]

—Some rate adaptive sensor systems require a special pacemaker lead.

VVI—Single chamber ventricular pacing

Indications: —Atrial fibrillation/flutter with atrioventricular block or slow ventricular response.

Contraindications: (a) Sick sinus syndrome
(b) Carotid sinus syndrome.
(c) Vasovagal syncope.

Advantages: —Single ventricular lead with standard pacemaker.

Disadvantages: —When used in the presence of normal atrial activity pacemaker syndrome is commonly caused by retrograde atrioventricular conduction.

—Loss of atrial synchrony may cause symptoms when used in the presence of normal atrial activity.

VVIR—Single chamber ventricular pacing with rate response

Indications: —As for VVI mode.

Contraindications: —As for VVI mode.

Advantages: —Rate response on exercise.

Disadvantages: —Pacemaker syndrome due to retrograde atrioventricular conduction.

—Loss of atrioventricular synchrony.

—Some rate adaptive sensor systems require a special pacemaker lead.

DDI—Dual chamber pacing without atrial tracking

Indications: —Sick sinus syndrome.

—Carotid sinus syndrome.

—Vasovagal syncope

Contraindications: —Isolated atrioventricular block

—Persistent atrial tachyarrhythmias.

Advantages: —Maintenance of atrioventricular synchrony.

—Protection from co-existent atrioventricular block.

—No pacemaker mediated tachycardias.[37]

—No tracking of atrial tachyarrhythmias.

Disadvantages: —No rate response.

—Two pacemaker leads required.

—Problems with retrograde atrioventricular block conduction not completely eliminated.[52]

DDIR—Dual chamber pacing without atrial tracking, but with a rate adaptive sensor facility

Indications: —Sick sinus syndrome.

Contraindications: —Isolated atrioventricular block.

—Persistent atrial tachyarrhythmias.

—Rate responsiveness not necessary in carotid sinus and vasovagal syndromes as this function is maintained naturally in these patients.

Advantages: —Maintenance of atrioventricular synchrony.

—Rate response on exercise.

—No pacemaker mediated tachycardia.

—No tracking of atrial tachyarrhythmias.

Disadvantages: —Two pacemaker leads required.

—Problems with retrograde atrioventricular conduction not completely eliminated.[52]

DDD—Dual chamber pacing with rate response due to atrial tracking

Indications: —Atrioventricular block with normal sinus node function.

Contraindications: —Persistent atrial tachyarrhythmias.

Advantages: —Restoration of atrioventricular synchrony.

—Rate response on exercise.

Disadvantages: Complex pacemaker requiring sophisticated followup.

—Two pacing leads required.

—Pacemaker mediated tachycardia may occur if retrograde P wave falls outside the atrial refractory period.[53 54]

—No rate response if sinoatrial node rate does not increase on exercise.

—Prolongation of atrial refractory period to prevent pacemaker mediated tachycardia results in lowering of the maximum attainable tracking rate and a rare possibility of pacemaker syndrome owing to retrograde atrioventricular conduction.[55]

—Behaviour of the pacemaker at the maximum tracking rate may be physiologically inept—for example, sudden development of 2:1 at atrioventricular block.

Many of these disadvantages can be overcome by careful programming of the pacemaker.

VDD—Ventricular pacing responding to atrial tracking

Indications: —As for DDD

Contraindications: —As for DDD.

Advantages: —As for DDD

Advantages—cont —Single pass atrioventricular lead may be used which is adequate for sensing P waves but cannot pace the atria.

Disadvantages: —As for DDD.

—Pacemaker behaves as VVI system at lower tracking rates, increasing the chances of . .

—Pacemaker syndrome and pacemaker mediated tachycardia.

DDDR—Dual chamber pacing with atrial tracking and additional rate adaptive sensor

Indications: —Atrioventricular block

—Sick sinus syndrome, especially if the sinoatrial node fails to increase its rate on exercise.

Contraindications: —Persistent atrial tachyarrhythmias

Advantages: —Maintenance of atrial synchrony

—Atrial tracking when feasible.

—Additional rate adaptive facility.

Disadvantages: —Complex programming and follow up.

—Two pacing leads required.

General considerations in rate adaptive sensor driven systems

Advantages:
Rate response on exercise independent of sinus node activity.

Disadvantages:
Sensor may require a special pacemaker lead.
Some sensor systems are based on less physiological measurements than others.
Sensor may be inappropriate in an individual patient (for example activity sensor in a bedbound patient; minute volume sensor in a patient with chronic lung disease).

Br Heart J 1991;66:192

BRITISH CARDIAC SOCIETY NEWSLETTER

Cardiologists support the concept of prevention of coronary disease, but few are enthusiastic or even active in the field. The British Heart Foundation symposium on Progress in the Prevention of Coronary Disease held in Edinburgh at the end of May had an excellent programme that attracted fewer participants than might have been expected: these included only one or two consultant cardiologists who were not themselves speakers Fortunately, other disciplines were better represented. The reasons for the indifference in our specialty are complex, and to a degree understandable But the symposium highlighted new and relevant progress—some that could be described as a hot topic—in epidemiology, pathology, haematology, biochemistry, genetics, and clinical cardiology The threads that have often seemed disparate and disjointed are now weaving a discernible pattern. It is still incomplete but it will increasingly influence many areas of good clinical practice. Cardiologists, though hard pressed by the burden of investigation and treatment for established disease, should no longer ignore it.

We will soon have more news of those registrar posts that will form part of the formal training programmes in cardiology. They will be only a few of them for two related reasons. First, we will have two training periods, equivalent to registrar and senior registrar, of three years each. It follows that we need only 60 registrars to equal the number of senior registrars (this includes paediatric cardiology) plus a small allowance for inevitable wastage. Few regions can expect more than one registrar appointment per year, and some of his or her time may well be spent in regional centres. Secondly, the Joint Planning Advisory Committee has made recommendations that will reduce appreciably the total number of career registrars irrespective of any training programmes: cardiology cannot be divorced from this process which is based on consultant opportunities. We question some of the premises and calculations, but we cannot deny the need for tighter control. The four senior registrar posts advertised from January to May 1991 attracted an average of 24 applicants seeking promotion from the registrar grade. Their mean age was 34 years. Those who were short-listed had spent about eight years as registrars, and were already very well trained. Many had an MD. What will happen to those who were not appointed, or indeed to those who did not reach the short list? Most will have been enticed into our specialty by the prospect of exciting research. In itself this may be good, but who can justify the frustration and the wasted years for the majority who will not achieve their goal? On the other hand, can the service survive the reduction in numbers that is now proposed? Only those who choose to remain totally ignorant of reality can believe that the shortfall can be made good by additional consultant effort, at least until we have many new consultant posts. If serious disruption is to be avoided, we will need to adopt several strategies including the appointment of competent overseas candidates to non-career training posts, perhaps the inclusion of cardiology in other specialist rotations, the use when possible of experienced hospital practitioners or clinical assistants and, above all, new appointments at consultant grade. As well as easing the burden directly, the eventual result of this last measure will be an increase in numbers within the training grades. The system may in time be self adjusting, but the process will take decades, not years, unless we have direct intervention with additional funding to bring our staffing levels more in line with those in most of the developed world.

We have special anxieties about women in cardiology, who face additional difficulties. Many need part-time training for which our allocation of senior registrar posts is top sliced, but few avail themselves of potential opportunities. The problem is not unique to cardiology—only 15% of *all* consultants are women. However, the figure for cardiology is 5%. One reason for the general difficulty in reaching consultant status is that the system for part-time training is poorly understood. We are grateful to Dr Angela Jones of the North West Thames Regional Health Authority for explaining the process. The scheme was set up in 1979 partly with the aim of providing posts for women doctors who wish to complete their training or work part-time while they raise their families. The posts are established on a personal basis and cease when the incumbent leaves the post. Senior registrars are funded from the regional health authority budget, but there is no obligation on the authority to do so. Our allocation of two whole-time equivalents should allow four individuals to benefit at any one time from part-time training, and we know from a survey we conducted a year ago that most centres would offer facilities if funding were on a supernumerary basis. The scheme is advertised annually in the journals, usually in the autumn. Applicants are considered by a National Assessment Committee, and successful applicants will be given manpower approval for nine months. During this time they must arrange educational approval which should be available after the supervising consultant has sent a training programme to the relevant Royal College. Funding is the next requirement in the complex process, but most will feel it prudent to liaise with their regional authority from the outset. Finally, the applicant must be interviewed by a modified appointments committee to demonstrate that she (or he) is of a similar calibre as a full-time applicant. A similar plan is also available at registrar grade, and at present this can be funded by the Department of Health. We are anxious that women who have embarked on a career in cardiology should use these facilities rather than abandon all hope of achieving their goal because of domestic pressures. Our postgraduate advisor will help those who are uncertain of how best to proceed, but trainees who wish to follow the part-time path may also wish to consult Jane Flint who is on our manpower committee with a special remit to help junior colleagues through the maze described above. We have written to all regional directors of public health and all postgraduate deans (in England) to point out the special problems that have to be faced by part-time trainees in cardiology, and the impracticality of posts depending on time shares. We hope that sympathetic help will be available even in this time of severe financial constraint.

Our Postgraduate Advisor, Howard Swanton, had drawn attention to the difficulties experienced by trainees in funding research posts, and has written a letter that forms the basis of what follows. We will try in future Newsletters to provide reminders of deadlines for grant applications. But please do not rely on us, we promise only to try! The information will be directed primarily at registrars who have not had research experience and who are seeking their first grant in a very competitive field. Hopeful applicants should obtain application forms and confirm closing dates by contacting the relevant research fund office at the addresses shown. All research projects must be approved by the local ethical committee if human subjects are involved.

The British Heart Foundation, 14 Fitzhardinge Street, London W1H 4DH (Tel: 071 935 0185; Fax: 071 486 1273). A booklet giving information on research awards can be obtained from Miss Valerie Mason, Research Fund Manager. She will be happy to give advice on the type of grant that might be appropriate. With the exception of Overseas Visiting Fellowships, applicants must be British citizens or have been resident in the United Kingdom for a minimum of three years. The fellowships committee meets quarterly to consider applications. Junior Research Fellowships are applicable to cardiologists who want to undertake one or two years research under direct supervision of a senior research worker The grant is for salary plus minor expenses. The head of the department must approve the application and state that funding for the research itself is already available. Intermediate Research Fellowships are offered for three years in the first instance. Applicants must have had research experience to qualify. For both types of fellowship, 10 copies of the research protocol are required together with a curriculum vitae. The closing date is 29 August for a meeting in October.

The Wellcome Trust, 1 Park Square West, London NW1 4LJ (Tel: 071 486 4902; Fax: 071 487 4915). A booklet on grants and support for research can be obtained from the address above. General inquiries can be addressed to Ms Sandra Carpenter. A limited number of Medical Graduate Research Training Fellowships are available for medical and dental graduates who should generally be under the age of 34. Grants are awarded for one, two, or occasionally three years. Initially applicants should submit a curriculum vitae, a brief 300–400 word document on the project, with the name of the supervisor, and the address where the work will be done. These and a completed application form should be sent to Dr David Gordon, Programme Director, at least three months before the work is due to start. Applications are considered four times a year, and short-listed candidates are interviewed.

Bristol-Myers Squibb, 141–149 Staines Road, Hounslow, Middlesex TW3 3JA (Tel: 081 572 7422). Application forms for Cardiovascular Fellowships Awards for 1992 can be obtained from Dr C H Dash, Vice President of Medical Affairs, Northern Europe Region, at the above address. Candidates should be citizens or residents of the United Kingdom, and should usually be at registrar or senior registrar level. Two awards are made annually. They support a research fellow for up to two years. The applications must include two letters of recommendation from individuals (usually senior cardiovascular physicians or cardiologists) familiar with the applicant's work. Previous experience is not essential. Short-listed candidates are interviewed. The closing date for applications is 31 October Awards are announced in January 1992 to start in July 1992.

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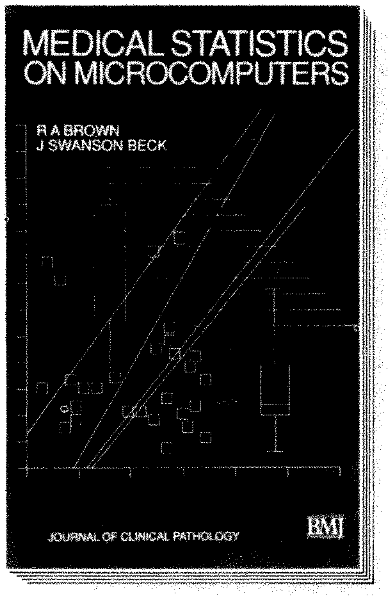

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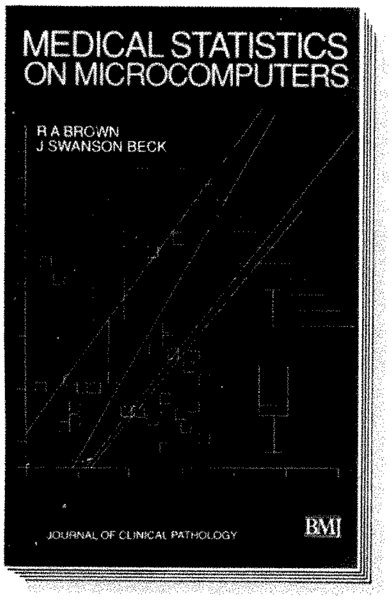

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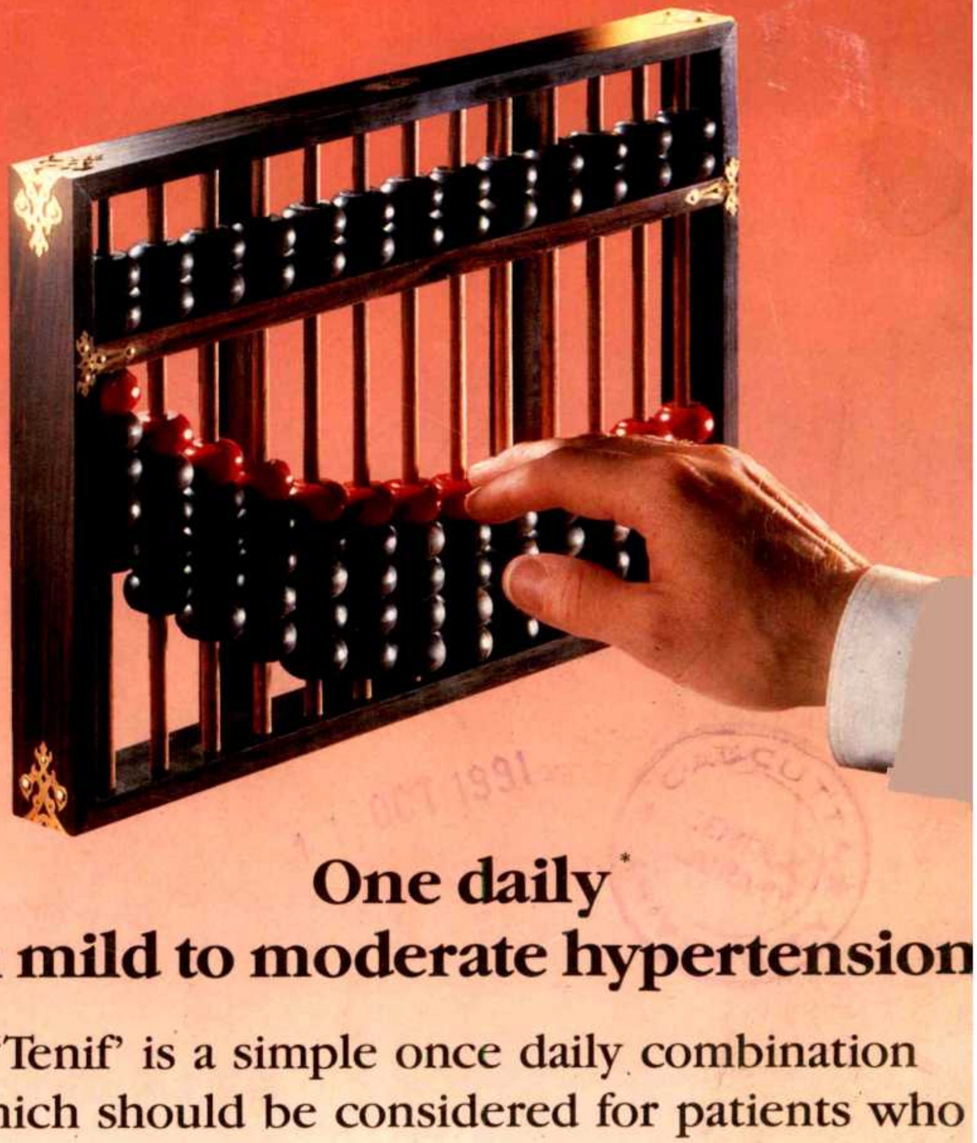

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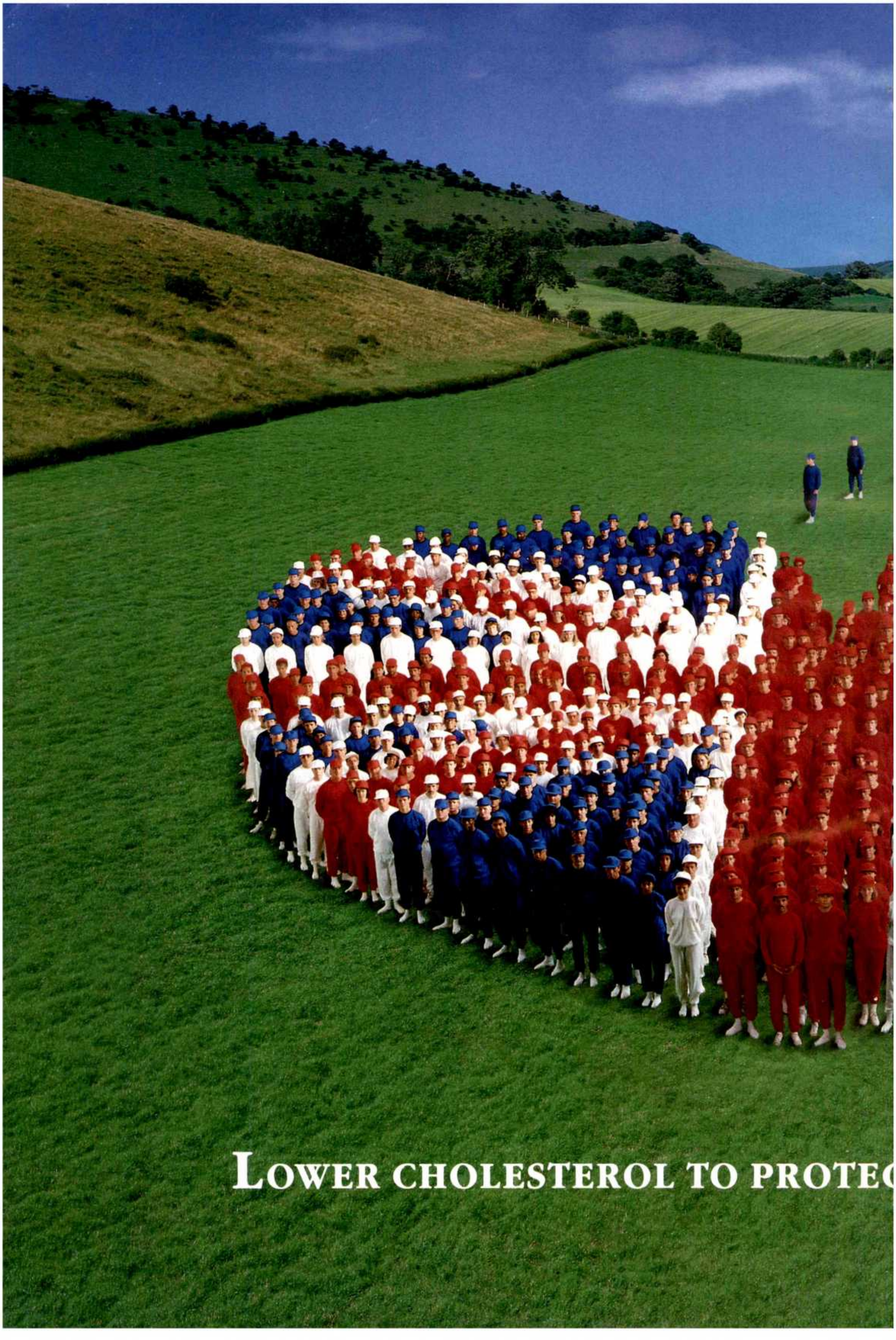
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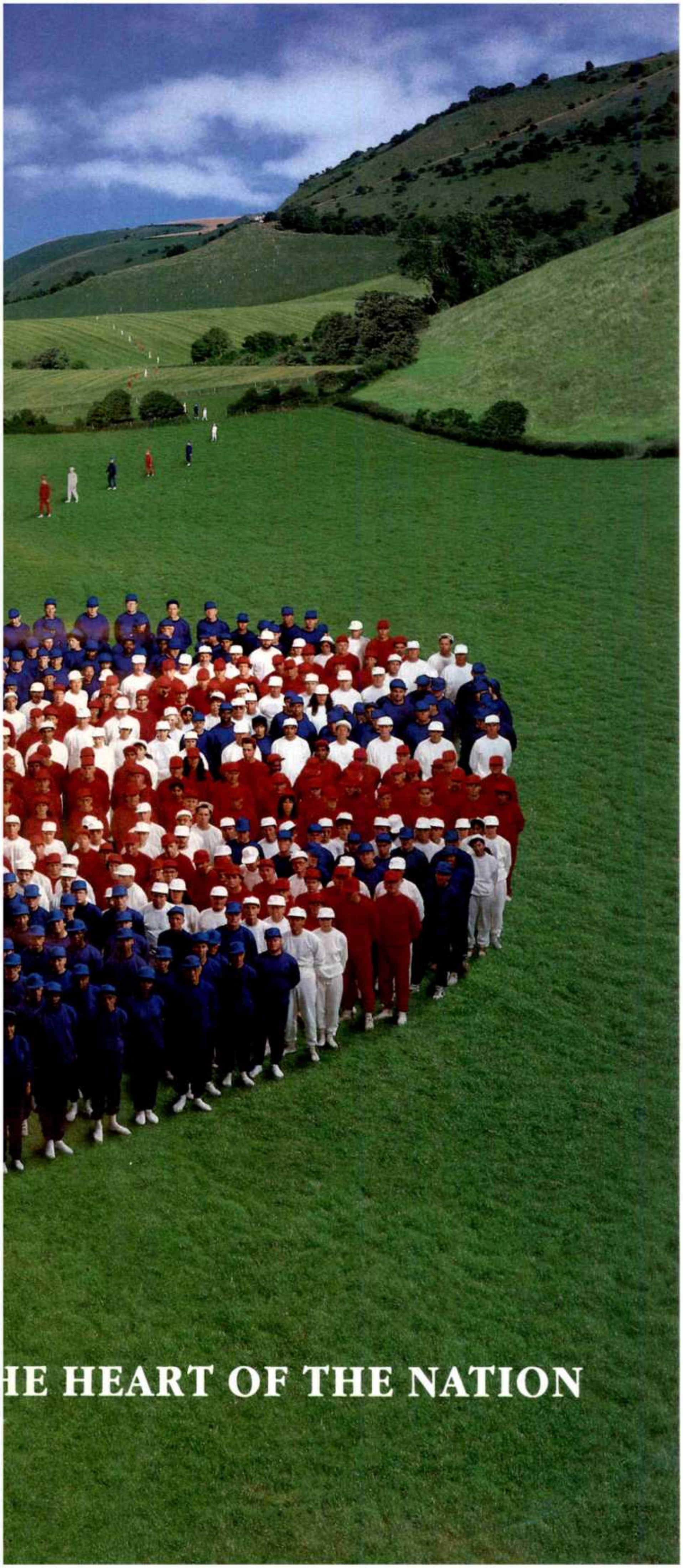
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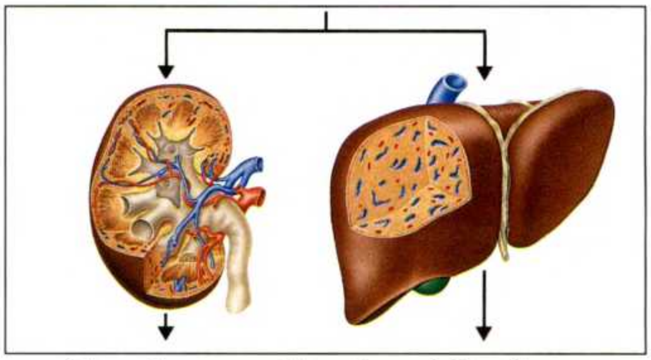

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Editorial

Management of patients with Björk-Shiley prosthetic valves

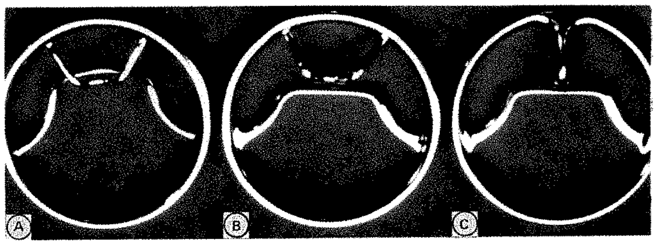
There are three basic types of Björk-Shiley valve (figure) that may be encountered in British patients. The much publicised hazard of strut fracture is effectively confined to the convexo-concave valve so in advising and managing patients electively it is helpful to be able to identify these valves. To some extent the identity of the valve can be determined from its date of implantation, but valves can be distinguished with certainty by their serial numbers when these are available. Otherwise it should be possible to identify them by radiological appearances.

Earlier valves

The original valve with a Delrin disc was implanted in about 85 000 patients between 1969 and 1979.[1,2] This was replaced with a pyrolitic carbon disc, known as a "spherical disc", that had a 60° opening angle. About 180 000 of these valves were implanted up to 1987. The serial numbers carry the prefix ABP for aortic valves and MBRP, MBUP, and MBP for mitral valves, where the first two initials (AB or MB) denote site and Björk design and the last initial (P) identifies the spherical disc pattern. (The U and R refer to details of the relation of the sewing ring to the annulus.) The two struts, which are visible radiologically, can be seen to overlap when the valve is imaged en face (Fig 1A). By 1979 there were only three reports of the disc escaping, out of a total of 90 000 implants. These were probably related to damage to the struts at the time of implantation.[1] Long term follow up in a large series was free of mechanical failure.[3]

The convexo-concave valve

Between 1976 and 1986 the convexo-concave (CC) valve was implanted.[2,4] In 1979 the new design was approved by the USA Food and Drugs Administration (FDA).[5] It was introduced in an attempt to improve the flow characteristics across the valve and reduce the risk of thrombus formation. The new 60° convexo-concave valve was implanted in about 82 000 patients before being withdrawn in April 1985 by Shiley. Case reports of strut fractures[6-8] include photographs of a consistent problem. The smaller strut had become detached from the annulus at the site of a weld and the disc escaped. In the meantime Shiley experimented with a 70° version of the same valve which unfortunately was even more prone to this problem. About one in eight of these valves was likely to fracture within seven years of implantation.[5] It was never released in the United States but about 4000 were implanted elsewhere between 1980 and 1983.[2] The codes for the CC valves are ABC, MBRC, MBUC, and MBC; again the final letter indicates the disc pattern and the numbers 60 or 70 denote the opening angle. The struts do not overlap when the valve is seen en face (Fig 1B). The valves particularly at risk are the 29 mm, 31 mm, and 33 mm mitral valves manufactured between February 1981 and June 1982. The overall risk of strut fracture is said to be 0·295% per annum.[9] More detailed estimates have been made by size and postoperative year[2] and are under 0·1% per annum in the low risk categories. These are likely to be underestimates because rapid deterioration or sudden death may well be attributed to other cardiac or non-cardiac causes and strut fracture will go undiagnosed.



Metallic component of the Björk-Shiley tilting disc valves. (A) The spherical model with "overlapping" struts when seen en face. Strut fracture extremely rare. (B) The convexo-concave valve. These are the valves at risk, particularly in the mitral site. (C) The monostrut Björk-Shiley tilting disc valve. No mechanical failures reported.

The monostrut valve

The monostrut valve was designed to overcome the strut fracture problem and seems to have done so successfully. It was introduced on to the market in 1983 but has never had FDA approval and is not available in the United States. The metal ring with its retaining struts is milled from a single piece. It can readily be identified on a penetrated *x* ray. The serial numbers begin with the letters ABMS, MBMS, and MBRMS; MS denotes monostrut.

The future

While it is easy to be wise after the event, it is hard to draw any firm conclusions for the future from this experience. Cardiac surgery is now routine and commonplace and patients and their physicians have come to expect perfect results. But there are many things that can go wrong and with long life expectancy after valve replacement many years in which they can go wrong. The United Kingdom Heart Valve Registry provides a mechanism by which a pattern of sudden death in valve recipients can be detected early.[10] Of course bench testing should be thorough before clinical use of a new device is contemplated and every care should be taken to do meticulous clinical follow up but because most patients who have heart valve replacements are expected to survive for more than 15 years[3 11] sooner or later fair wear and tear will take its toll of mechanical devices performing 42 million cycles per year. The annual incidence of problems related to the mechanical valve itself is minute in comparison with the number of patients who die each year of endocarditis, valve thrombosis, embolism, anticoagulant related haemorrhage, and natural progression of disease in the heart and elsewhere.[12] Virtually all mechanical valve recipients will die with an intact prosthesis. Without innovation we cannot make further progress and yet we know that it has now become extremely difficult for anyone to pioneer a new valve or even a small modification of an old one. If "the industry is so punished by the press and professional critics that innovation is stifled and the risk for failure becomes too great to continue" then we will see no further progress in valve design. This situation seems to be upon us in the USA.[13]

The more immediate problem is how should a clinician deal with patients who have these valves in place. The first obvious piece of advice is that in any patient with an artificial valve who deteriorates, first suspect the valve. If strut fracture has occurred the only hope is emergency reoperation so no time should be lost in referring the patient to the nearest cardiac surgical unit. Strut fracture can be diagnosed by screening alone.

The commoner problem is the large number of patients who remain well but are afraid. First of all the valve should be identified by serial number and if this is not available screening may be justified to identify spherical and monostrut valves which are not prone to this problem, so that the patient can be given this reassuring news without delay. Symptoms and clinical change must be dealt with on their merits but the individual can be strongly reassured about the theoretical risk of strut fracture in the future.[9] For patients with a convexo-concave valve, while action may not be justified, reassurance must be a little more guarded because one in 30 of those with a mitral valve that is 29 mm or larger is at risk of death due to strut fracture. The alternative of electively replacing the valve carries a far worse risk. The risk of death with reoperation on the mitral valve was nearly 16% in 206 cases operated on in United Kingdom units in 1989 (70% confidence interval 13% to 19%), that is more than three times that of a first operation (J Cleland. United Kingdom Cardiac Surgical Register, personal communication). Reoperation doubles the risk in aortic valve replacement from just over 4% to nearly 9% (70% CI 6% to 12%). Of course it could be argued that these figures are those for clinically indicated reoperation including patients with catastrophic states such as endocarditis or sudden valve failure. Nevertheless, the difference between the risk of strut fracture and that of repeat valve surgery is sufficiently great that elective replacement of these valves for fear alone is unjustifiable.

And what is the legal position? Shiley have publicly indicated their willingness to meet claims from patients who have experienced strut fractures and they have settled directly to avoid protracted legal cases. Whether this is a generous and humane gesture or an economically sound strategy is open to interpretation but we all know that the law is a slow and bitter way of gaining compensation for medical injury. On the other hand Shiley will "vigorously defend" anxiety claims and believe that a "functioning valve is no basis for a claim".

I thank Mr J Cleland for supplying figures from the United Kingdom Cardiac Surgical Register and Mr Philip Ayers of Shiley for providing illustrations and technical data.

TOM TREASURE

St George's Hospital,
Blackshaw Road,
London SW17 0QT

1 Bjork VO, Henze A. Ten years' experience with the Bjork-Shiley tilting disc valve *J Thorac Cardiovasc Surg* 1979;78·331–42

2 Hiratzka LF, Kouchoukos NT, Grunkemeier GL, Miller DC, Scully HE, Wechsler AS Outlet strut fracture of the Bjork-Shiley 60° convexo-concave valve. current information and recommendations for patient care. *J Am Coll Cardiol* 1988;11:1130–7.

3 Bloomfield P, Wheatley DJ, Prescott RJ, Miller HC Twelve-year comparison of a Bjork-Shiley mechanical heart valve with porcine bioprostheses *N Engl J Med* 1991;324 573–9

4 Nightingale SL. Shiley heart valve physician and patient notification program *JAMA* 1991;265:847

5 Brahams D. Bjork-Shiley heart-valve failures *Lancet* 1990;336:619–20.

6 Sethia B, Quin RO, Bain WH Disc embolisation after minor strut fracture in a Bjork-Shiley mitral valve prosthesis *Thorax* 1983;38.390–1.

7 Ibarra F, Gutierrez A, Martinez F, Carreras L, Lopez C, Alonso-Lej F. Fracture of the outlet strut of a Bjork-Shiley mitral prosthesis. emergency operation with survival. *J Thorac Cardiovasc Surg* 1984;87 315–8.

8 Jaumin P, Ponlot R, Schoevaerdts J-C, Brasseur L, Chalant C-H. Strut fracture of the Bjork-Shiley aortic valve *J Thorac Cardiovasc Surg* 1984,88·787–91

9 Advising patients with artificial heart valves *Lancet* 1990;336 152

10 Taylor K Acute failure of heart valves *BMJ* 1988,297:996–7

11 Sethia B, Turner MA, Lewis S, Rodger RA, Bain WH. Fourteen years' experience with the Bjork-Shiley tilting disc prosthesis. *J Thorac Cardiovasc Surg* 1986,91 350–61

12 Treasure T. Which heart valves should we use? *Lancet* 1990,336.1115–7

13 Collins JJ. The evolution of artificial heart valves. *N Engl J Med* 1991,324 624–6.

Br Heart J 1991,66:335–6

Editorial

Heart valve surgery in the United Kingdom: present practice and future trends

The surgery of heart valve disease raises many questions. Should we conserve or replace the diseased valve? What should the replacement valve be—a homograft, a bioprosthetic valve, or a mechanical valve? Isn't valve disease becoming less common anyway?

Test reports, clinical comparisons, and longitudinal follow up studies, particularly those focusing on the very latest artificial heart valve are reminiscent of car tests in motoring magazines—with the latest model, incorporating state of the art technology, giving superior performance (under manufacturer's test conditions)... and costing just that bit more. This plethora of scientific advice about which valve to choose can be confusing and individual reports are not necessarily widely representative or capable of extrapolation.

Comprehensive information on the pattern of operations for heart valve replacement has been available on a national basis in the United Kingdom since 1986, when the United Kingdom Heart Valve Registry was established. This registry, funded by the Department of Health, receives data from all National Health Service cardiac surgical units in the United Kingdom and provides unique information on the changes in patient numbers, on demographics data, and on the preferred types of artificial valves currently being implanted by cardiac surgeons in the United Kingdom.

Although the national registry cannot yet be expected to answer the vexed question, "what artificial heart valve should we use?", it already provides answers to other questions.

What number of heart valve replacement operations are carried out in the United Kingdom?

About 5000 artificial valves are implanted each year in the United Kingdom, in just over 4500 patients. These totals remained remarkably stable in the period 1986–89 (table 1). They are similar to those reported in the United Kingdom Cardiac Surgical Register—4791–4873 heart valve operations per year in the years 1977–1980 (J Cleland, personal communication). This remarkable consistency in numbers of valve operations in the United Kingdom contrasts with the considerable increase in coronary graft operations over the same time period. In the late 1970s fewer than 4000 coronary graft operations were carried out each year. By 1985 the annual figure had risen to over 12000 operations.

Table 1 Number of patients and heart valve implants in United Kingdom 1986–89

Year	*Patients*	*Valves*
1986	4665	5217
1987	4525	5087
1988	4706	5204
1989	4569	5058

Table 2 Heart valve implants by type and position in 1986–89

Year	*Single*	*Double*	*Triple*	*Aortic*	*Mitral*	*Tricuspid*
1986	4216	490	7	2817	2353	47
1987	4104	475	11	2779	2258	50
1988	4216	482	8	2859	2287	58
1989	4101	458	12	2934	2086	38

Single valve replacement procedures account for around 90% of all valve operations. Ten per cent are double valve replacements, and triple valve replacement operations are rare, accounting for less than 0·2% of all valve procedures. As with total numbers of implants, these figures have shown remarkably little change over the past few years (table 2).

Aortic valve replacement is now the commonest procedure: it accounts for around 60% of procedures. Mitral valve replacements account for almost 40%, and only around 1% of valve replacements are tricuspid replacements.

These data suggest that the expected overall reduction in valve surgery numbers as rheumatic valve disease became less common has not in fact happened. A reduction in rheumatic abnormalities has presumably been balanced by an increase in valve replacement procedures for degenerative valve disease. This could also explain the increasing proportion of aortic over mitral replacements over the past five years. (aortic 54%–59%, mitral 45%–40%).

What artificial valves *do* we use?

This has changed considerably over the past four or five

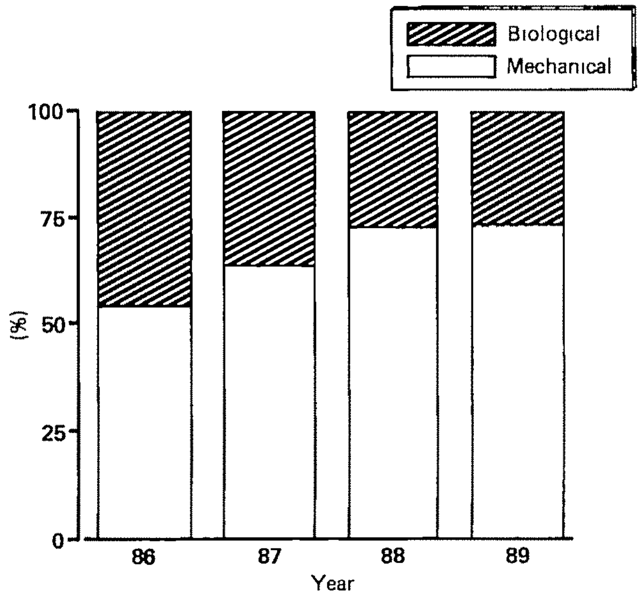


Figure 1 Percentage use of biological and mechanical heart valve prostheses in the United Kingdom (1986–89) (data from United Kingdom Heart Valve Registry)

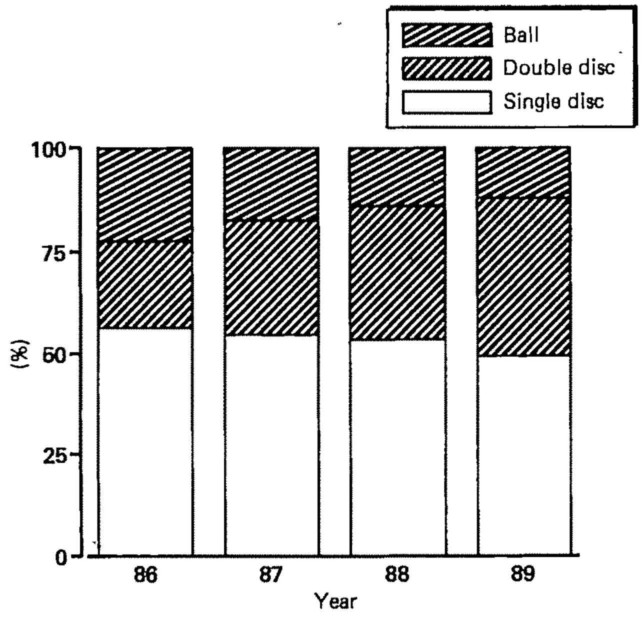


Figure 2 Percentage use of main types of mechanical heart valve prostheses in the United Kingdom (1986–89) (data from United Kingdom Heart Valve Registry).

years. In 1986 about 54% of valves implanted in the UK were mechanical valves, compared with 46% bioprosthetic valves. Homograft valves account for less than 1% of total implants. In 1987–88 an increased preference for mechanical valves resulted in a 70% to 30% split between mechanical and bioprosthetic valves. The situation seems to have reached a steady state with little further change over the past two years (fig 1).

There are also trends in the use of particular valve types. Over the past four years single disc valves were the most commonly used mechanical valves. The use of ball valves declined and there was a significant corresponding increase in the use of bi-leaflet valves (fig 2). For the year 1989, the figures were 48% single leaflet, 37% bi-leaflet, and 15% ball valves. In the bioprosthetic valve group, the preference for porcine over bovine pericardial valves has increased since 1986 when 75% of bioprosthetic valves implanted were porcine. By 1989 the proportion of pericardial valves had fallen to 15%, presumably reflecting doubts over the long term durability of pericardial valves.

These data indicate a clear shift in surgical preference in the period 1986–89 towards mechanical valves. No single factor is obvious in determining this trend, but it seems likely that the perceived requirement for re-operation with bioprosthetic valves convinces surgeons and cardiologists more than the potential of avoiding anticoagulation in some patients. Whether this perception can be supported by hard data is quite another matter. It is interesting, however, to see such a clear trend, particularly when patients are getting older (37% over 65 years in 1989) and when 60% of all replacements are aortic valves, more often than not in patients in sinus rhythm.

What of the future?

Whatever else happens, it seems certain that the average age of patients requiring heart valve surgery will continue to increase. It has been estimated that 40% of valve surgery patients in the 1990s will be over 65 years of age. Although valve surgery in the elderly patient may be performed with very acceptable results, operative mortality and postoperative morbidity have been shown to be increased. Careful preoperative assessment and identification of major risk factors in elderly patients should improve results further.

Conservative valve surgery, particularly in the mitral position, is likely to increase as surgeons gain more experience in the techniques pioneered by Carpentier *et al* in France[1] and Cosgrove *et al* in the USA.[2] Currently, conservative procedures account for around 10% of all mitral valve operations but only 0·5% of aortic procedures. Homograft aortic valve replacements make up around 2% of all aortic replacements. It seems likely, therefore, that most heart valve surgery in the United Kingdom population will continue to require the replacement of affected valves by some form of artificial valve.[3] The current preference for mechanical valves may well continue at present levels, although this part of the whole equation is difficult to predict.

Long term information from the national registries should provide reliable data upon which such choices may be made in the future. At the very least, registry information will let us know the extent of the correlation, if any, between the valves we think we should use and the valves we actually do use.

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1 Carpentier A, Chauvaud S, Fabiani JN, *et al* Reconstructive surgery of mitral valve incompetence. *J Thorac Cardiovasc Surg* 1980;79·338–48.
2 Cosgrove DM, Chavez AM, Lytle BW, *et al.* Results of mitral valve reconstruction. *Circulation* 1986;74·82–7
3 Taylor KM. Acute failure of artificial heart valves. *BMJ* 1988;297.996–7.

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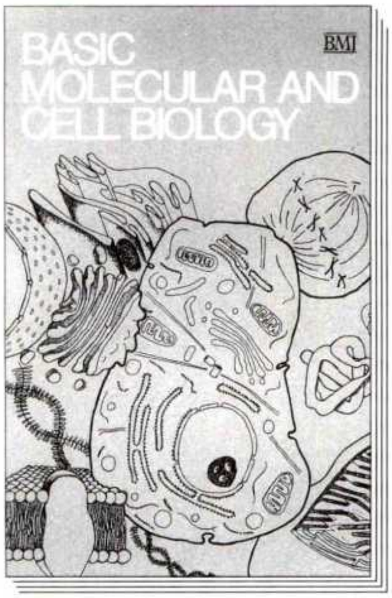
REFERENCES: 1. White WB, Dey HM and Schulman P. Am Heart J 1989; 118: 782-795. **2.** Kannel WB. Am J Med 1983; **75**: 4-11.



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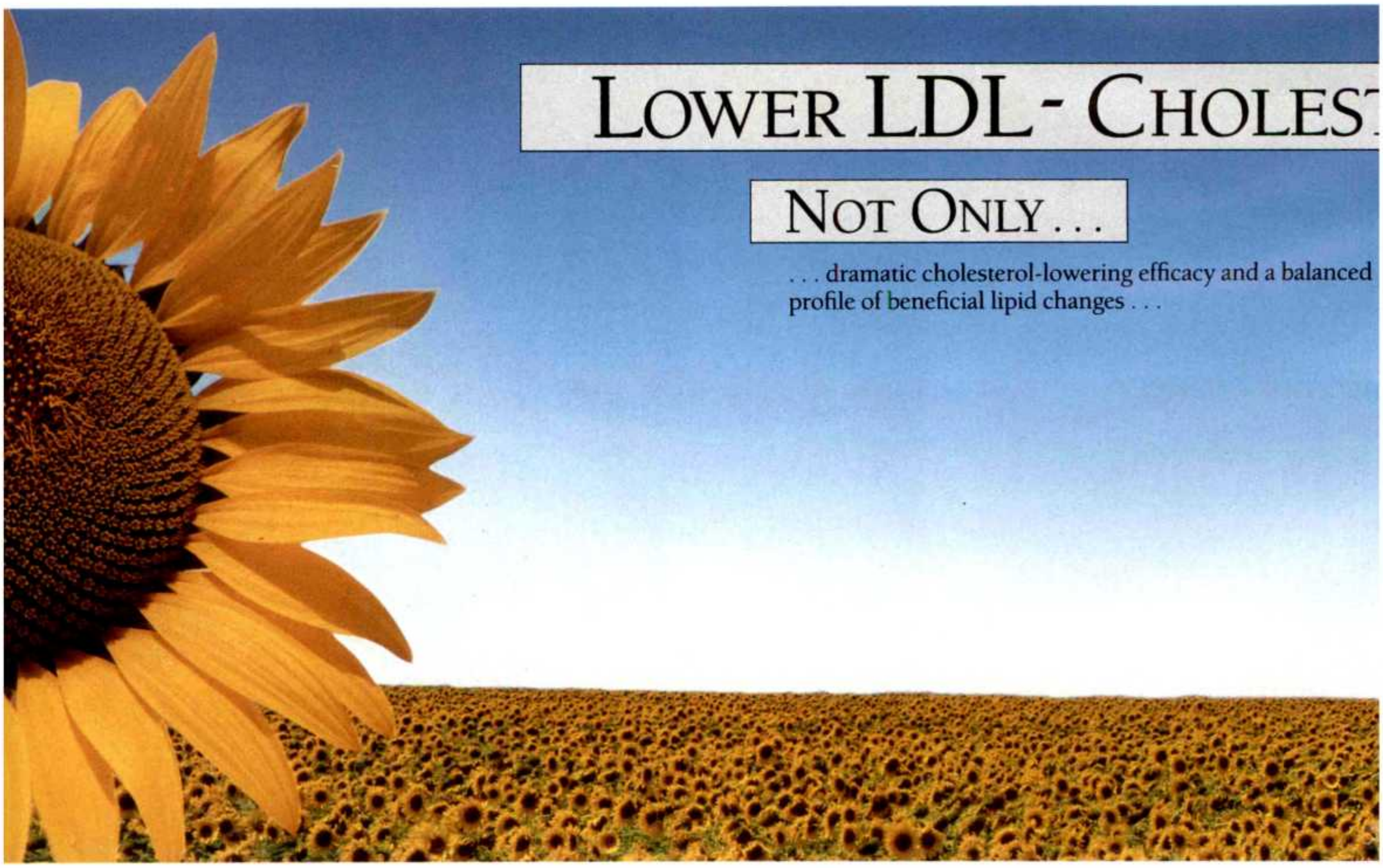
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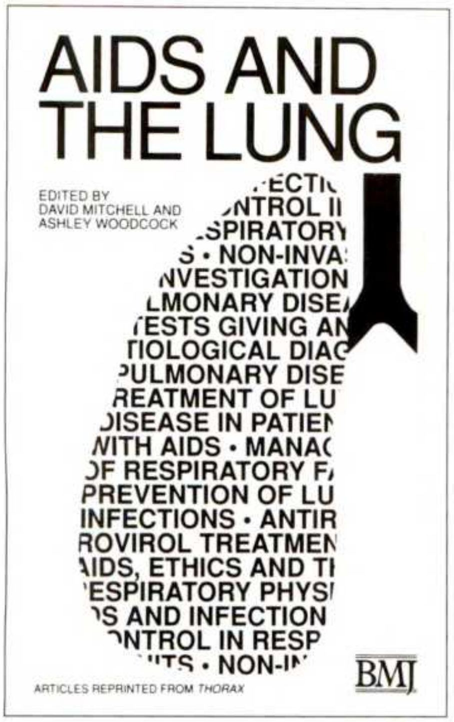
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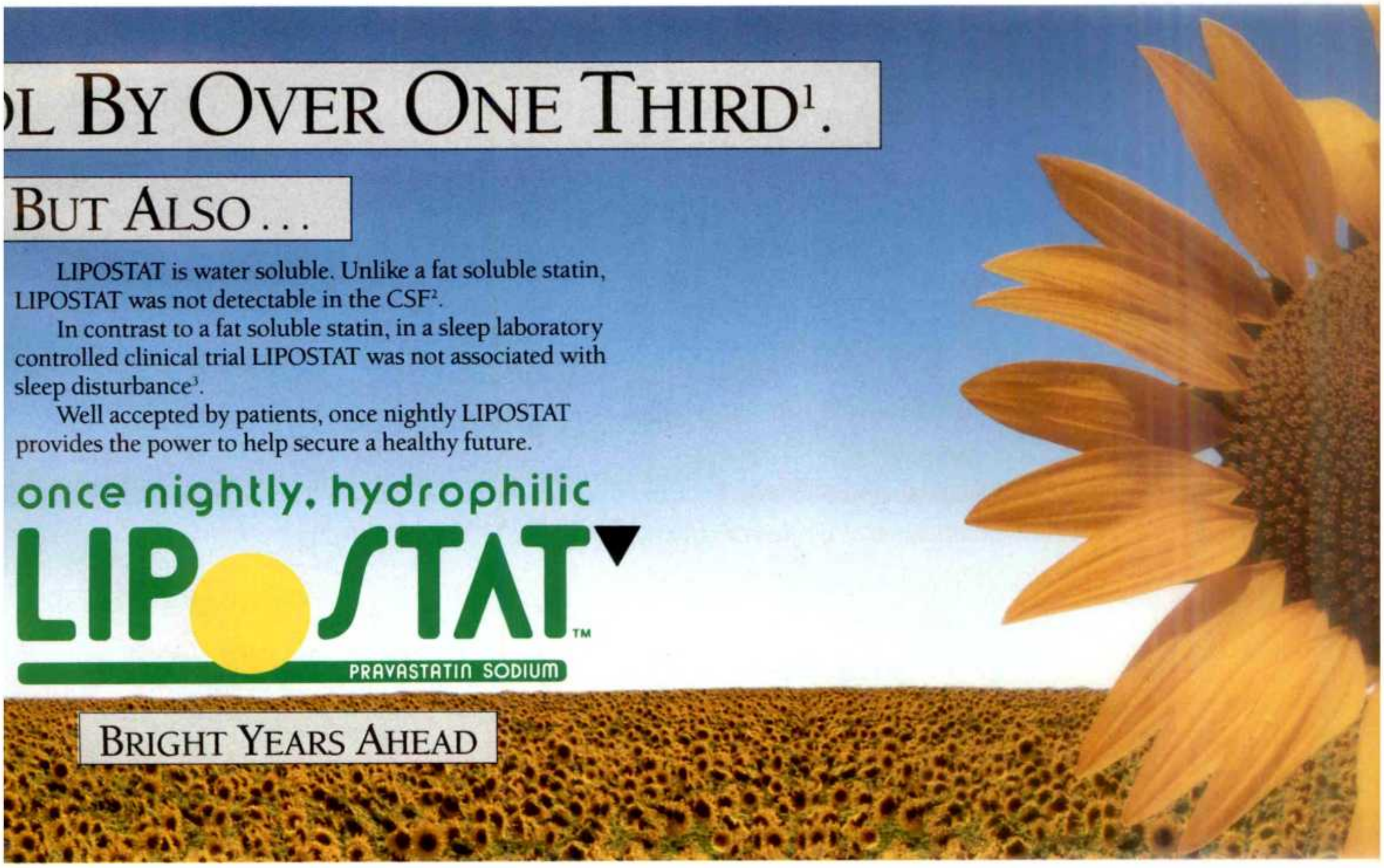

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References
1. Data on file. In trials LIPOSTAT demonstrates an LDL-cholesterol reduction of up to 34% from baseline values (after 8 weeks, 40mg nocte).
2. Botti RE et al. Clin Neuropharm 1991; **14** (3): 256-261
3. Bixler EO. Round Table Discussion, Lipid Management; Pravastatin and the Differential Pharmacology of HMG-CoA Reductase Inhibitors. Proceedings of a panel discussion held in London on 5th July 1989. Royal Society of Medicine Services Round Table Series 1990; 16: 32-40

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LOREX

TTJBD61

Br Heart J 1991;66.337–45

ORIGINAL ARTICLES

Short and long term results after intracoronary stenting in human coronary arteries: monocentre experience with the balloon-expandable Palmaz-Schatz stent

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Abstract

***Objective*—Intracoronary stenting was designed to overcome acute complications after percutaneous transluminal coronary angioplasty and to achieve a reduced rate of restenosis, both of which are major limitations of this well accepted method for treating coronary heart disease. This report describes the experience at one centre with the implantation of balloon-expandable Palmaz-Schatz stents and focuses on device related complications and the short and long term angiographic outcome.**

***Design*—A retrospective data analysis.**

***Patients*—Stenting was attempted in 50 patients. Restenosis after an initially successful angioplasty procedure, inadequate postangioplasty results, saphenous coronary bypass stenoses, and bail-out situations were regarded as indications.**

***Main outcome measures and results*—In 49 of 50 attempted patients 61 stents (1–4 per patient) were implanted. Delivery problems occurred in three patients and were successfully overcome in two patients. Bail-out situations were successfully managed in 16 patients. Complications included acute thrombus formation within the stent immediately after implantation in one patient, which was successfully treated by thrombolysis. One patient was sent for bypass surgery the day after implantation; another died 10 days after implantation for unknown reasons. Subacute stent thrombosis occurred in seven patients 5–9 days after implantation and was successfully treated by thrombolysis or balloon angioplasty in five patients. Bleeding complications occurred in nine patients, five of whom required blood transfusions. Angiography showed long term vessel patency after 4–6 months in 31 (76%) of the 41 patients who were followed up, restenosis in six (14%), and reocclusion in four (10%). Late restenosis or reocclusion was found in five (15%) of 33 patients with a single stent in contrast to five (63%) of eight patients with multiple stents.**

***Conclusions*—Balloon-expandable intracoronary stenting is a feasible method for treating the acute complications of balloon angioplasty. It reduced the rate of restenosis for single stent implantation. Subacute thrombotic events must be regarded as previously unknown and serious complications.**

Although percutaneous transluminal coronary angioplasty (PTCA) is widely accepted as the best intervention for the treatment of coronary heart disease in patients presenting with stable and unstable angina, serious limitations continue despite the progress that has been made. In particular, the incidence of acute complications after balloon angioplasty—such as dissections, vessel rupture, and acute thrombosis with or without consequent myocardial infarction—has been reduced but they remain unpredictable factors.[1–15] Furthermore, long term success is limited by the rate of late restenosis, which ranges from 14% to 44% depending on patients population and, primarily, on the definition of restenosis.[1–3 10 15–18] Intracoronary stenting was designed to overcome the acute complications of balloon angioplasty and reduce the number of requests for surgical interventions,[19–22] and also to reduce the late restenosis rate.[22–29] Different stent types have been developed and implanted into human coronary arteries after previous animal studies had produced promising results.[19–22 25–37]

We report experience at one centre of the implantation of balloon-expandable Palmaz-Schatz stents in human coronary arteries.

Patients and methods

PALMAZ-SCHATZ STENT

This balloon-expandable stent consists of two stainless steel meshes connected via a single bridge to improve flexibility (fig 1). Balloon inflation expands the stent up to the maximum balloon diameter pressing it against the vessel wall. Only low inflation pressures are necessary to achieve complete stent expansion, which reduces the risk of balloon rupture.[35 36] The expanded stent remains in position after balloon deflation.

PATIENTS

Intracoronary stenting was attempted in 50 patients (table 1) (two women and 48 men, aged 41–76) presenting with at least one of the

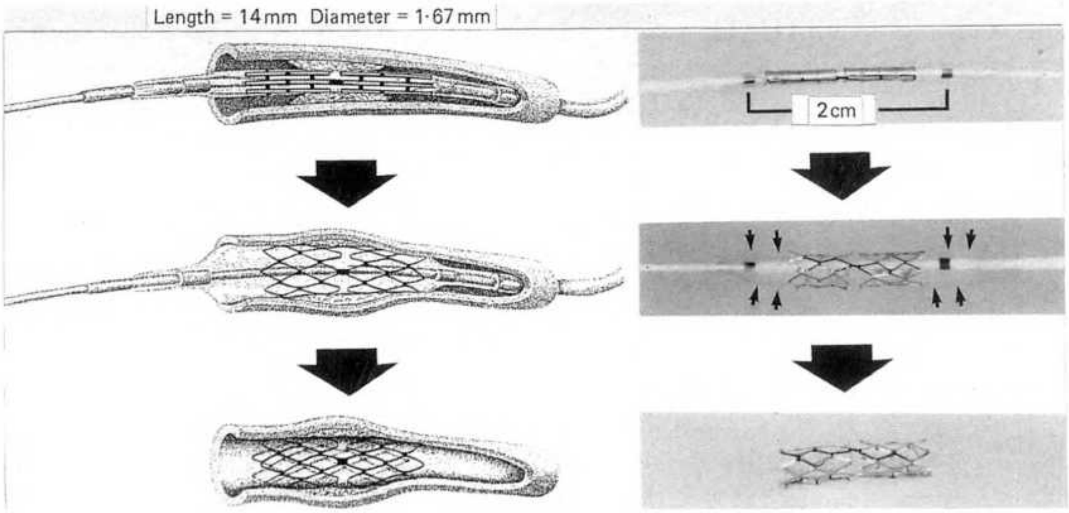

Figure 1 Balloon-expandable Palmaz-Schatz stainless steel stent before balloon inflation (upper panel), after balloon inflation (middle panel), by the expanded balloon (small black arrows), and after balloon deflation and withdrawal (lower panel).

following indications: (*a*) restenosis after an initially successful coronary angioplasty procedure (31 patients); (*b*) inadequate angiographic result after balloon angioplasty with or without limitation of distal contrast medium run off (15 patients); (*c*) bail-out situations (16 patients with symptomatic dissections); (*d*) coronary bypass stenosis (one patient).

All patients gave their informed consent for the coronary balloon angioplasty procedure, for the stent implantation if at least one of the defined indications developed, and for a follow up coronary angiogram 4–6 months after im-

Table 1 Details of 50 patients in whom implantation of balloon-expendable Palmaz-Schatz stents was attempted

Case	Age	Sex	Risk factors	AP CCS	Previous PTCA	Previous MI	Target lesion	Collaterals	Indication for stenting
1	47	M	H, IIa, N	II	LAD 88	88	LAD S	III	R
2	41	M	IIa, N	I	LAD 89	88	LAD Occ	III	R
3	60	M	—	III	LAD 87	81	LAD S	II	R, D, B
4	69	M	IIa	III	LAD 87	—	RCA Occ	III	R, D, B
5	66	M	IIa, N	I	RCA 88	88	RCA S	II	R, D, B
6	58	M	IIa, N	III	LAD 87	87	LAD S	II	R
7	65	M	—	III	—	87	RD1 Occ	III	D, B
8	53	M	—	II	LAD 88	—	LAD S	III	R
9	67	M	N	IV	—	—	RCA S	II	Inad res
10	57	M	H, N	III	LAD 88	88	LAD S	III	R
11	55	M	O	III	LAD 88	—	LAD S	II	R
12	55	M	O, IIa	II	LAD 88	—	LAD S	II	R
13	47	M	IIa, N	II	LAD 88	—	LAD S	II	R, D, B
14	76	M	O, IIa, N	III	LCx 88	87	LCx S	II	Inad res
15	58	M	O, N	III	LAD 89	88	LAD S	III	R, D, B
16	68	M	IIa, N	I	RIM 89	—	RIM S	II	R, D, B
17	68	M	H, IIa, N	III	RCA 86	85	RCA S	II	Inad res
18	55	M	DM, O, N	II	—	—	LAD S	II	D, B
19	64	M	H, O	II	—	—	LAD S	II	D, B
20	70	M	O, IIa, N	III	—	89	RCA S	II	D, B
21	64	M	DM, O, IIa, N	III	LAD 89	—	LAD Occ	II	R
22	56	M	N	II	LAD 88	—	LAD Occ	III	R, inad res
23	61	M	IIa, N, O	II	LAD 88	88	LAD S	III	R
24	66	M	N, IIa	III	—	—	RCA Occ	II	Inad res
25	50	M	N	III	LAD 88	88	LAD S	II	R, D, B
26	54	M	IIa, N	III	LAD 88	—	LAD S	II	R
27	56	M	N	III	LAD 87	—	LAD S	II	R
28	59	M	O, IIa, N	II	LAD 89	88	LAD S	II	Inad res
29	61	M	O, IIa	I	LAD 88	89	LAD Occ	III	Inad res
30	69	F	IIa	II	—	88	LAD S	II	D, B
31	61	M	O, IIa, N	II	LAD 89	—	LAD S	III	R, inad res
32	61	M	H, O, N	II	LAD 89	89	LAD S	II	R
33	60	M	H, A, IIb, N	II	LAD 89	88	LAD S	II	R
34	69	M	H, N	III	—	—	LAD S	II	Inad res
35	64	M	O, IIb, N	I	LAD 89	—	LAD S	III	R
36	49	M	O, IIa, N	IV	LAD 89	—	LAD Occ	II	R
37	64	M	O, H, IIa	II	LAD 88	—	LAD S	II	R, D, B
38	63	M	H, IIb, N	III	RD1 88	87	RD1 S	II	R
39	64	M	H, O, IIb	III	LAD 89	—	LAD S	II	Inad res
40	58	M	N	II	—	89	RCA S	II	Inad res
41	49	M	—	III	LAD 89	89	LAD S	III	R
42	55	M	H, IIb, N	I	RCA 89	89	RCA S	III	R
43	52	M	H, O, V, N	IV	LAD 89	—	LAD S	II	R, D, B
44	61	M	H, N	II	LAD 89	—	LAD S	II	R, inad res
45	60	M	H, O, IIb, N	III	—	—	RCA S	—	Inad res
46	70	F	H, O	III	—	—	LAD S	—	D, B
47	51	M	IIa, N	II	—	—	SBG S	—	SBG S
48	75	M	—	III	—	89	RCA S	—	D, B
49	69	M	H, N	III	LAD 89	86	RCA S	I	Inad res
50	53	M	—	III	RCA 87	84	RCA S	II	R, inad res

H, hypertension; N, cigarette smoking; O, obesity; IIa, IIb, and V, type of hyperlipoproteinaemia according to Fredrickson; AP, grade of angina pectoris according to the Canadian Cardiovascular Society (CCS); LAD, left anterior descending artery; RCA, right coronary artery; LCx, left circumflex artery; RD1, first diagonal branch; RIM, intermediate branch; SBG, saphenous bypass graft; R, restenosis; D, dissection; B, bail-out; Inad res, inadequate angioplasty result; PTCA, percutaneous transluminal coronary angioplasty; MI, myocardial infarction; Occ, occlusion; S, stenosis.

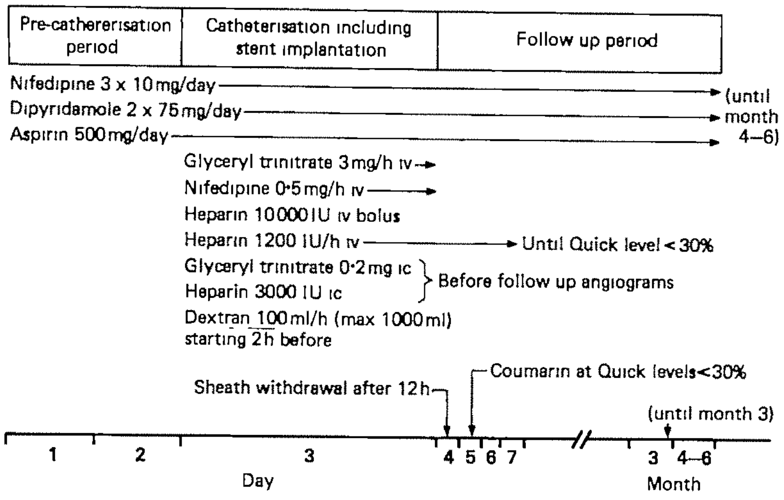
Pre-catheterisation period
Catheterisation including stent implantation
Follow up period
Nifedipine 3 x 10 mg/day
Dipyridamole 2 x 75 mg/day
Aspirin 500 mg/day
(until month 4–6)
Glyceryl trinitrate 3 mg/h iv
Nifedipine 0·5 mg/h iv
Heparin 10000 IU iv bolus
Heparin 1200 IU/h iv
Until Quick level < 30%
Glyceryl trinitrate 0·2 mg ic
Heparin 3000 IU ic
Before follow up angiograms
Dextran 100 ml/h (max 1000 ml) starting 2 h before
Coumarin at Quick levels<30%
Sheath withdrawal after 12 h
(until month 3)
1
2
3
4
5
6
7
Day
3
4–6
Month

Figure 2 Medical treatment of patients undergoing intracoronary stenting. iv, intravenous; ic, intracoronary.

plantation to investigate the long term outcome.

PROCEDURE

Patients were treated with aspirin (500 mg) (Colfarit), nifedipine (3 × 10 mg) (Adalat) and dipyridamole (2 × 75 mg) (Persantin forte) each day starting two days before the investigation (fig 2). In the catheterisation laboratory they were given 100 ml/h dextran before the procedure, an intravenous bolus injection of 10 000 IU heparin, and continuous infusion of 1200 IU/h heparin, 0·5 mg/h nifedipine, and 3 mg/h glyceryl trinitrate (Perlinganit). After left ventricular angiography coronary angiograms of the left and right coronary arteries were performed in several projections to show the target lesion and the collateral supply. Angioplasty of the target lesion was then performed with 9F guiding catheters (Medtronic, USA) and balloon catheters (ACX, ACS, and Hydro-Cross; Edwards) with diameters ranging from 2·0 to 3·5 mm. Intracoronary injections of 0·2 mg glyceryl trinitrate and 3000 IU heparin were given before the follow up angiogram. If one of the defined indications was present we decided to implant a balloon-expandable Palmaz-Schatz stent. The Judkins guiding catheters were replaced by 9F Amplatz guiding catheters via a 3 m guide wire where possible. Then the Palmaz-Schatz stent was mounted between the radiopaque markers of a 3·0 mm balloon catheter (USCI), which has a balloon length of 2·5 cm and can be inflated up to 14 atm (fig 1). The markers are needed to aid positioning of the stent because the mesh is not radiopaque. The long balloon covers the ends of the stent struts and prevents them damaging the vessel. The balloon with the mounted stent was then inserted into the target lesion and inflated to pressures up to 12 atm for 5–10s.

Another angioplasty was performed within the stent in 24 of 49 patients to achieve some overdilatation of the stented vessel segment and good fixation of the stent to the vessel wall (table 2). Finally, follow up angiograms were performed in different oblique projections. The sheaths were withdrawn after 12 h and heparin infusion was continued for 48 h. All patients were given continuous nifedipine, dipyridamole, and high dose aspirin until late follow up angiograms were performed after 4–6 months (fig 2). Starting with patient 8, coumarin was also given and heparin infusion was continued until Quick values <30% were obtained. Because of the effect on subacute thrombosis after stent implantation reported by Schatz *et al* this anticoagulation treatment was continued for three months.[29 37]

QUANTITATIVE CORONARY ANGIOGRAPHY

Coronary luminal narrowing was estimated in two orthogonal views that give the best images of the target lesion. These views were also used to assess short and long term vessel patency. We calculated the absolute and relative minimal stenosis diameters according to the assumptions of Brown *et al*,[38] and we used the guiding catheter as a reference. Restenosis was defined as a reduction of >50% in the lumen diameter or a loss of >50% of the initial result.

STATISTICAL ANALYSIS

Minimal stenosis diameters are expressed as mean (1SD). We used analysis of variance, Student's t test, the χ^2 test, and Fisher's test, as appropriate, to test for significant changes. A probability of $p < 0.05$ was regarded as significant.

Results

Figure 3 shows a successful stent implantation in a right coronary artery (patient 45). The indication for the implantation was an inadequate postangioplasty result after repeated balloon angioplasty with larger balloon catheters, longer inflation times, and increased inflation pressures. The severity of stenosis decreased considerably after stent implantation and the improvement persisted even after six months.

PRACTICABILITY

We successfully implanted 1–4 stents per patient in 49 of 50 patients in whom intracoronary stenting was attempted. In one (patient 19) it was impossible to position the balloon catheter with the mounted stent into a predilatated but dissected lesion of the left anterior descending artery. Two other patients required additional angioplasties with larger balloons (3·5 mm diameter) before stent delivery could be successfully performed.

COMPLICATIONS

Acute thrombosis within the stent was seen immediately after implantation in one patient (patient 46), who had a dissected lesion of the anterior descending artery after angioplasty and a history of unstable angina. This patient was treated by an intracoronary bolus injection of 300 000 IU urokinase and additional intravenous infusion of 1·5 million IU urokinase for 30 minutes. A non-Q wave myocardial infarc-

Table 2 *Individual angiographic results, balloon sizes, number of implanted stents, and complications in 50 patients*

	Minimal stenosis diameter				*Max balloon diameter*				
Case	*Pre PTCA (mm)*	*Post PTCA (mm)*	*With stent (mm)*	*4–6 mnth (mm)*	*PTCA (mm)*	*Stent implant (mm)*	*Stent dilatation (mm)*	*Implanted stents (n)*	*Complications*
1	0 7	3 2	3 6	3 1	3	3 5	—	1	—
2	0	2 4	2 8	0	3	3	—	2	—
3	0 5	1 5	3 5	3 2	3	3	—	1	—
4	0 2	2 5	3 4	0	3	3·5	—	4	—
5	1 5	3 5	3 5	1	3	3 5	—	3	—
6	1	2·5	2 9	—	3 5	3	—	1	Death
7	0 2	1 5	3	3	3	3	3	1	—
8	1 5	2	3 6	1	2 5	3	3 5	1	AVF
9	1	2	3 3	3 3	2 5	3	3·5	1	—
10	0 7	2	3 4	2 3	2 5	3	3 5	2	—
11	1 8	2	3 5	3 5	2 5	3	3·5	1	GI bleed
12	1 3	2	3 4	2 6	2 5	3	3·5	2	—
13	1 5	2	2·8	2 6	3	3	—	1	Ging bleed
14	1	1 5	3 5	2 4	3 5	3 5	—	1	Ging bleed
15	1	2	3 5	0	3 5	3 5	3 5	3	SAT
16	1	1 5	3	2 7	3	3	—	1	—
17	1 5	1 5	3	0	2·5	3	—	2	SAT
18	0 5	2 5	3 5	—	3	3 5	—	1	Dissec + CABG
19	0 8	2 0	—	—	3	—	—	—	Impl impos
20	2 5	3	3 5	3·5	3 5	3 5	—	1	—
21	0 2	1 5	3	3	3	3	—	1	SAT
22	0	1 5	2 8	2 5	3	3	3	1	Ging bleed
23	0 9	2	3 5	3 2	3	3	3 5	1	—
24	0	2	3 4	3 3	3 5	3	3 5	1	—
25	1	2 4	3 5	2 5	3	3	3 5	1	GI bleed
26	0 9	2	3 5	3 5	3	3·5	—	1	AVF, SAT
27	1 5	2 5	3 5	2 5	3	3	—	1	—
28	1	1 5	3	0 8	3	3	3 5	1	—
29	0 2	1 8	3	2 8	3	3	—	1	—
30	1 3	2	3 3	1 1	3	3	3 5	1	—
31	0 8	1	3 4	3 4	3 5	3 5	—	1	—
32	1 7	2	3 5	3 4	3 5	3	3 5	1	—
33	1 8	2 3	3	0 9	3	3	—	1	—
34	1 5	2 4	3 2	—	3	3	3 5	1	—
35	1 2	2 5	3	—	3	3	—	1	—
36	0	2	3	3	3	3	—	1	SAT
37	1 7	2 5	3 4	2 9	3	3	3 5	1	—
38	0 8	2	3	3	3	3	3 5	1	—
39	0 9	1 8	3	3	3	3	—	1	—
40	1 3	1 5	3	2 5	3 5	3	3 5	1	—
41	0 4	2 1	3 7	3 1	3 5	3 5	4	1	—
42	0 4	2 3	3	2 5	3	3	—	1	—
43	0 8	1 8	3 5	—	3	3	3 5	1	—
44	1	1 8	3 5	2 8	3	3	3 5	2	Ging bleed
45	1 5	2	4	4	3	3 5	4	1	—
46	0 8	1 5	3 1	3 1	3	3	—	1	Thrombus
47	1 3	2	2 8	0 5	3	3	—	1	—
48	1 5	1 6	3 5	—	3	3	3 5	1	AVF
49	1 2	1 9	2 5	—	3	2 5	—	1	SAT
50	1 8	1 8	3 5	—	3	3	3 5	1	SAT, CABG
Mean	1 00	2 02	3·26	2 39	3 00	3 10	3 50	—	—
(SD)	0 57	0·47	0 31	1·15	0 36	0 23	0·20	—	—

PTCA, percutaneous transluminal coronary balloon angioplasty; AVF, arteriovenous fistula, GI bleed, gastrointestinal bleeding, Ging bleed, gingival bleeding; SAT, subacute stent thrombosis; CABG, coronary artery bypass grafting, impl impos, implantation impossible, dissec, dissection.

tion with a maximum rise in creatinekinase to 400 IU/l developed. A follow up angiogram after 24 h showed vessel patency without any persisting thrombus formation.

One patient (patient 18) was sent for elective bypass surgery 24 h after stent implantation because of persisting angina but without changes on electrocardiogram or in creatine kinase activity. In this patient, who presented with a stenosis of the left anterior descending coronary artery near to the origin of the first diagonal branch, the guide wire could be placed only in the diagonal branch and not in the distal left anterior descending coronary artery. After balloon angioplasty there was a long dissection at the site of dilatation that altered blood flow in the distal part of the left anterior descending coronary artery even after successful stent implantation.

Symptomatic thrombotic complications including vessel closure occurred in seven patients 5–9 days after stent implantation. These were regarded as subacute complications in view of the interval since implantation. Table 3 shows individual data on stent implantation, the time of subacute vessel closure, the medication, and the coagulation indices for these seven patients. Suboptimal anticoagulation or antiaggregation at the time of vessel closure was found in two of seven patients, which means that either coumarin, aspirin, and/or dipyridamole were not given, or given in inadequate doses. Reopening of the stented vessel was achieved by thrombolysis or mechanical recanalisation and balloon angioplasty in five of seven patients. The two patients in which these measures failed were sent for bypass surgery—one immediately and the other four months later because of persisting angina and an abnormal stress test despite good collateral supply of the target vessel. Three patients developed Q wave myocardial infarctions and two non-Q wave myocardial infarctions. Late follow up coronary angiograms after stent implantation, performed in four of five thrombolytically or mechanically recanalised

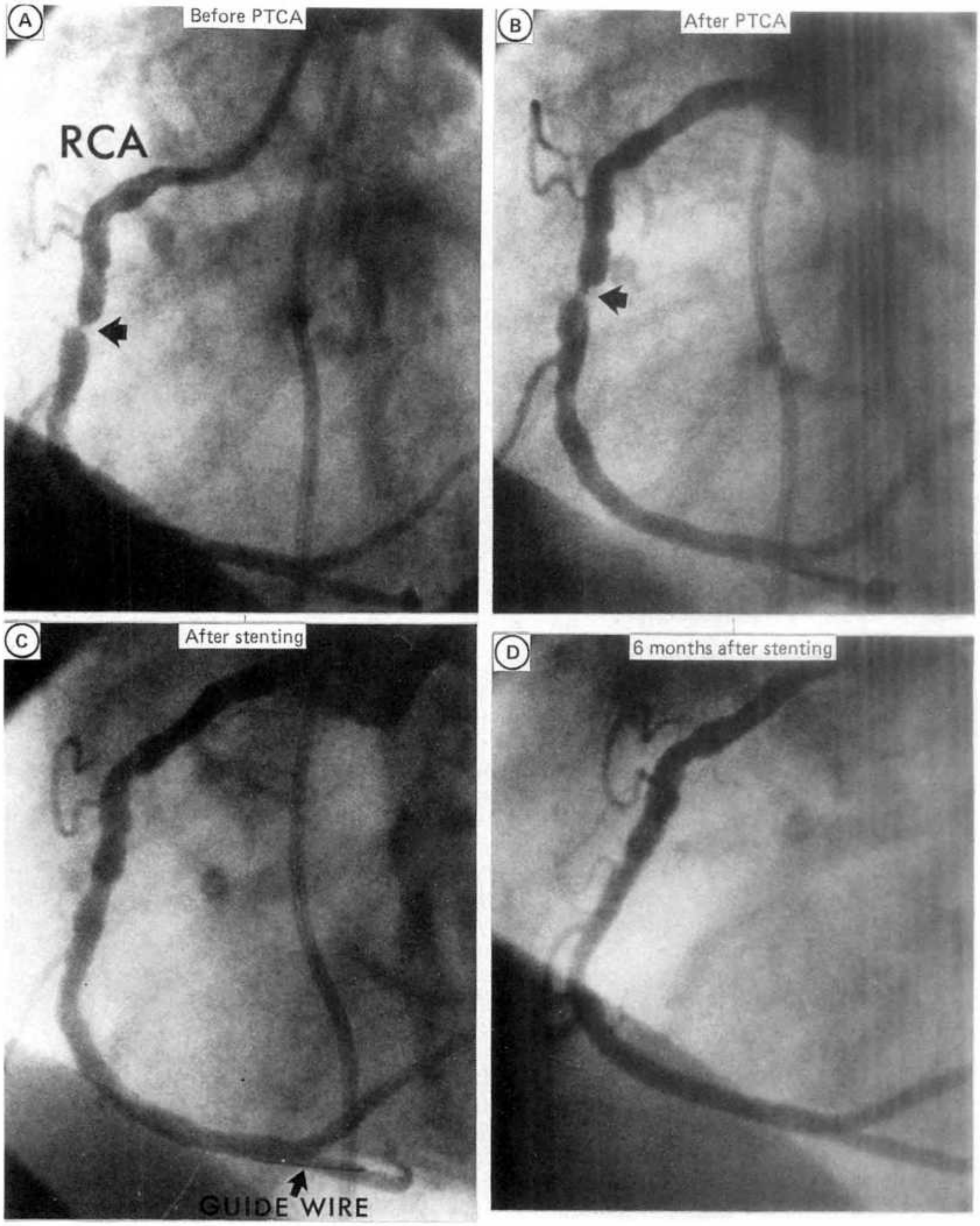

Figure 3 Angiograms of a patient with a subtotal stenosis of the right coronary artery (RCA) before and after balloon angioplasty (PTCA) and the short and long term angiographic results after implantation of a balloon-expandable Palmaz-Schatz stent.

patients, showed long term vessel patency in three. The other presented with late reocclusion and was successfully recanalised by angioplasty.

One patient (case 6) died out of hospital 10 days after implantation of an unknown cause. Necropsy was not performed.

Major bleeding complications requiring blood transfusions occurred in five patients (10%) (gastrointestinal bleeding in two patients during the follow up period and haematoma in the groin with arteriovenous fistulae in three patients after sheath withdrawal). Minor bleeding complications such as gingival bleeding occurred in four patients (8%).

QUANTITATIVE CORONARY ANGIOGRAPHY

Visual inspection of the coronary angiograms after stent implantation showed smooth vessel wall segments without any wall irregularities in most cases, in contrast to the usual appearance after balloon angioplasty. Especially in patients with large and symptomatic dissections after balloon angioplasty the intimal and medial flaps were successfully wrapped against the vessel wall in 15 of 16 leaving no angiographic signs of residual stenosis.

Table 2 shows the individual results of the quantitative analysis of the minimal luminal narrowing before and after balloon angioplasty, after intracoronary stenting, and four to six months later together with data on maximum balloon sizes for balloon angioplasty and stent implantation. The mean (1 SD) minimal luminal diameter after balloon angioplasty was 2·02 (0·47) mm compared with 1·00 (0·57) mm before angioplasty ($p < 0{\cdot}001$). After stent implantation there was a further increase in luminal diameter to 3·26 (0·31) mm ($p < 0{\cdot}001$). In contrast, the mean maximum balloon size for angioplasty was 3·00 (0·36) mm

Table 3 Individual procedure-related data, medication, and anticoagulation variables of seven patients with subacute thrombosis after implantation of balloon-expandable Palmaz-Schatz stents

No case	*Target lesion*	*Collaterals*	*Stents*	*Time of SAT (days)*	*Medication*			
					Coumarin	*Heparin (IU/h)*	*Aspirin (mg)*	*Dipyridamole*
15	LAD sten	III	3	9	+	—	500	+
17	RCA sten	II	2	7	+	—	500	+
21	LAD occl	II	1	6	+	—	100	+
26	LAD sten	II	1	8	+	—	500	+
36	LAD sten	II	1	9	+	—	—	+
49	RCA sten	I	1	5	+	1000	500	+
50	RCA sten	II	1	5	+	1200	500	+

Sten, stenosis; occl occlusion, nQ MI non-Q wave myocardial infarction; Q MI. Q wave myocardial infarction, CK, creatine kinase MB

and for stent implantation 3·10 (0·23) mm, giving balloon:vessel ratios of 0·9 and 0·95, respectively.

There was a 33% decrease in the maximum achievable diameter measured after balloon angioplasty but almost no loss after stenting (fig 4).

RESTENOSIS

Forty three (89%) of the 47 suitable patients had follow up angiograms (fig 5). Five symptom free patients refused scheduled late coronary angiography. Angiograms were performed in 36 (84%) of the 43 suitable patients four to six months after stenting and in seven (16%) before this scheduled date because of thrombotic complications. In the group of 36 patients who had the follow up angiography, 28 (78%) showed vessel patency and eight (22%) restenosis or reocclusion. Angiograms were obtained four months after stenting in five of seven patients with subacute thrombosis. In four of these patients thrombolysis or mechanical recanalisation was successful and in another it was not. Thus 41 (84%) patients had long term follow up angiograms after four to six months that showed open vessels without restenosis in 31 patients (76%), restenosis in six patients (15%), and reocclusion in four patients (9%), of whom one had successful and another unsuccessful recanalisation, which was attempted because of subacute thrombosis after stenting.

Only three of eight patients with multiple stents had patent vessels four to six months after stenting. One had late restenosis and four had late reocclusion. In contrast 28 (85%) of the 33 patients with single stents had patent vessels four to six months after stenting; three of them had had successful thrombolysis or mechanical recanalisation because of subacute stent thrombosis. Late restenosis was found in five (15%) of 33 patients with single stent implantation (p < 0·02 compared with multiple stent implantation). No late vessel occlusion occurred in these patients.

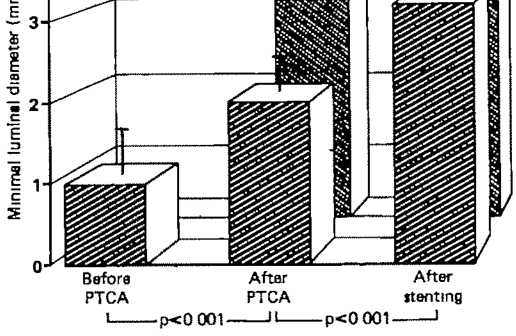

Figure 4 Minimal luminal diameters (mean (1 SD)) before and after balloon angioplasty and after implantation of balloon-expandable Palmaz-Schatz stents compared with the maximum balloon diameters used.

Mechanical recanalisation of chronically occluded coronary arteries was attempted in eight of the 50 patients. In six this achieved long term vessel patency; in two there were late reocclusions.

Coumarin had been given to 35 of the 41 patients who had long term follow up coronary angiography—seven (20%) with late restenosis or reocclusion and 28 (80%) patients in whom the vessel remained patent. In those not treated with coumarin long term restenosis or reocclusion was found in three patients and long term vessel patency in two (no significant difference compared with the coumarin treated group). One patient in this subgroup died 10 days after implantation.

Discussion

Restenosis after an initial successful coronary angioplasty procedure, inadequate postangioplasty results, coronary venous bypass stenosis, and bail-out situations are commonly accepted indications for stent implantation.[19,21–24,27–32] The rate of successful implantation was 98%, which is comparable to the results of other groups and to the rate of success for pure balloon angioplasty procedures.[2,4,29,31,37] Although the balloon with the mounted stent becomes somewhat stiffer, we were able to pass most lesions. The importance of sufficient predilatation was demonstrated in two patients who required another angioplasty before stent delivery was successful. Nevertheless, in tortuous lesions it can be difficult if not impossible to pass the lesion with this device, as occurred in one patient.

Acute complications were less common after stent implantation than after coronary balloon angioplasty. Severe complications such as acute thrombosis or dissections resulting in acute vessel closure were reported in 1·1—8% of patients after coronary balloon angioplasty.[5,7,11–13] Only one of our patients had acute thrombosis immediately after stent implantation. This patient had unstable angina. The reported rates of thrombosis and acute vessel *ıble 3 continued*

AT III (%)	PTT (s)	Quick (%)	TT (s)	Therapy	ECG	CK Max (IU/l)	CK MB (IU/l)
—	52	14	17	PTCA	—	479	8
—	54	30	15	—	—	—	—
—	49	27	16	PTCA	nQ MI	700	75
68	20	10	24	Thrombolysis	Q MI	2180	380
88	8	22	18	Thrombolysis	Q MI	983	98
77	120	17	120	PTCA	nQ MI	567	41
76	80	77	120	CABG	Q MI	809	41

ıction. See footnotes to tables 1 and 2 for other abbreviations.

closure after angioplasty are higher in patients with unstable angina.[8,9]

Sixteen of 50 patients needed a bail-out procedure after balloon angioplasty, because they had symptomatic coronary dissections with angiographically documented flaps. The flaps were wrapped against the vessel wall in most cases and there was a considerable reduction in symptoms and ischaemic electrocardiographic changes. Previous investigators have discussed the relation between the extent of dissections and the rate of acute complications including vessel closure and the request for urgent bypass surgery.[15,18] Vessel wall irregularities such as intimal and medial flaps alter blood flow and promote thrombus formation. There were no acute vessel closures or requests for urgent bypass surgery among our patients, even those with symptomatic dissections. In one patient who had a long dissection after angioplasty of a lesion of the left anterior descending artery a single stent was implanted but a residual distal flap persisted and altered blood flow in the distal part of the vessel even after stenting. This patient was sent for elective bypass surgery the next day. This case emphasises the application of "over the wire techniques" for stent implantation with proper positioning of the wire in the distal part of the target vessel and not in side branches, especially those that originate next to the target lesion. The long wire technique allows easy exchange of balloon catheters for angioplasty and stent delivery even in the presence of dissections. It also provides a stable back up when the stent device is advanced.

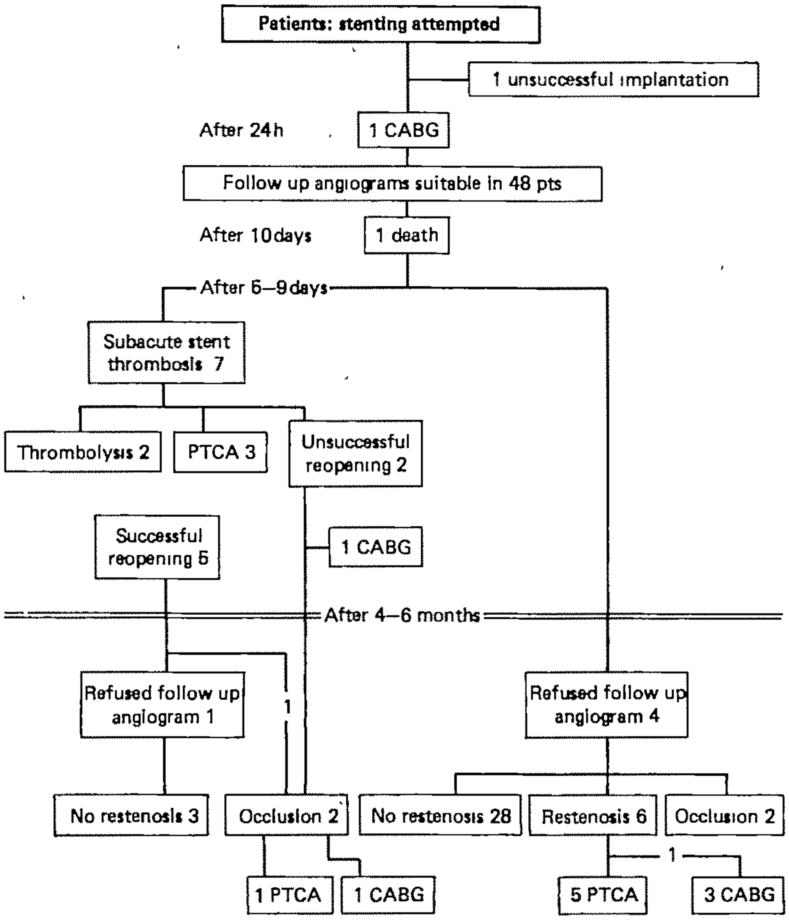

Figure 5 Flow chart of the results of restenosis in 50 patients, in whom intracoronary implantation of balloon-expandable Palmaz-Schatz stents was attempted.

Subacute stent thrombosis five to nine days after implantation must be regarded as a new device-related problem. It was reported in 18% of 39 patients not treated with warfarin and in 0·6% of 174 patients treated with warfarin who had a Palmaz-Schatz stent implanted.[29,37] Serruys *et al* reported 25 (21 within the first 14 days) subacute vessel closures in 105 patients receiving a self-expandable Medinvent stent.[28,39] This confirmed previous reports.[24] Similar results have been reported for Gianturco and Wiktor stents. The rate of subacute vessel closures was 10%. Schatz,[29,37] recommended that all patients with stent implantation should be treated with long term medication including high dose aspirin (500 mg/day). dipyridamole, and additional coumarin to prevent subacute thrombotic complications. Nevertheless, seven (14%) of our patients had a subacute stent thrombosis. Retrospective analysis showed that anticoagulation or antiplatelet aggregation treatment had been inadequate in two of seven patients. On the other hand, five patients who were given optimal medical treatment also had subacute stent thrombosis. In five patients subacute vessel closure occurred soon after heparin was stopped. Although routine serum coagulation indices (prothrombin ratio, activated partial thromboplastin time, Quick levels) were optimal, stopping heparin after several days treatment may have promoted increased rebound coagulation. More detailed analysis of the patients' individual coagulation state showed that the prothrombin fragments F1 and F2 are better indices for predicting subacute stent thrombosis.[40,41] Also, coagulation factor II is a better index of coumarin induced anticoagulation than the Quick value especially before intravenous heparin is stopped.

Bleeding complications occurred in nine (18%) patients; five needed blood transfusions. This was a somewhat higher rate than that associated with coronary angioplasty alone.[2,13] The most likely explanation is the extended anticoagulation and antiplatelet aggregation treatment.

One patient died of an unknown cause out of hospital 10 days after implantation. Necropsy was not performed. This patient did not receive coumarin. There was no evidence of stent related death or myocardial infarction asso-

Table 4 Different definitions of restenosis applied to the late angiographic results after implantation of balloon-expandable Palmaz-Schatz stents

Definition of restenosis	*Rate of restenosis (%)*					
	Stent implantation		*Single stent implantation*		*Multiple stent implantation*	
	With SAT (n = 41)	*Without SAT (n = 36)*	*With SAT (n = 33)*	*Without SAT (n = 30)*	*With SAT (n = 8)*	*Without SAT (n = 6)*
>50% diameter reduction and >50% loss of the post-stent result	24	22	15	17	63	50
>30% decrease in diameter at follow up compared with the post-stent result	29	28	21	17	63	50
>70% diameter reduction and >50% loss of the post-stent result	24	22	15	17	63	50
Decrease in diameter at follow up to within 10% of the predilatation diameter	24	22	15	17	63	50
>50% loss of the post-stent result	27	22	18	17	63	50
>0 72 mm reduction in diameter at follow up compared with the post-stent result	37	36	24	27	88	83

SAT, subacute stent thrombosis.

ciated with vessel closure although the timing does not differ from that of subacute stent thrombosis. One stent related death has been reported from the central registry for the Palmaz-Schatz stent.[29 37]

There was a 33% loss in the maximum achievable diameter after balloon angioplasty compared with almost no loss after stenting, though the maximum balloon:vessel ratios were similar. This is a commonly known limitation of coronary balloon angioplasty and is in part brought about by the elastic recoil forces of the coronary arteries.[42–44] Balloon-expandable stenting improved the angiographic results of the lesion dimensions by inhibiting these elastic recoil forces. The residual area stenosis after implantation of self-expandable Medinvent stents was reported to be about 36%[43] and the residual diameter stenosis 22% immediately afterwards and 17% after 24 hours,[44] which is considerably higher than our results for mean residual diameter stenosis after balloon-expandable stenting, which was less than 5%.

Despite the small number of patients studied we analysed our data to obtain information about the rate of late restenosis after coronary stent implantation. The rate of restenosis and reocclusion was calculated to be 24% compared with about 30% after coronary balloon angioplasty.[1 17] Because the data for restenosis depend on the definition used, we also calculated the rate of restenosis for other frequently used definitions (table 4). Patients with single stent implantation showed better long term vessel patency than patients with multiple stents; this finding accords with Schatz's data.[37]

We conclude that wherever possible multiple stent implantation should be avoided for a single coronary lesion. The possible reasons for the poor long term outcome of multiple coronary stent implantation are an increased thrombophilia and induction of intimal proliferation, especially when there is an overlap of two adjacent stents.[25 29] Additional treatment with coumarin did not tend to influence the rate of late restenosis—in contrast to the results reported earlier.[37] However, only seven patients were not treated with coumarin compared with 41 patients who were. This may explain the outcome. Nevertheless, long term coumarin treatment (for at least three months) must be reconsidered because we found no evidence that it inhibited subacute stent thrombosis or late restenosis while bleeding complications were more common.

Statistical analysis did not identify any other risk factors for late restenosis in these patients, such as balloon size, inflation pressure, duration of inflation, absence or presence of dissections, or the resulting vessel diameters.

Intracoronary implantation of balloon-expandable Palmaz-Schatz stents is a new, highly feasible interventional technique. Management of acute complications after coronary balloon angioplasty was especially successful. Currently the long term outcome seems to be open, though we did find a significantly lower restenosis rate when single stents were used. In our opinion, subacute stent thrombosis must be regarded as a new, serious complication and a limitation of this promising method, which our results suggest cannot be counteracted by extended anticoagulation and antiplatelet aggregation treatment but by improved coagulation monitoring.

1 Gruntzig AR, King SB, Schlumpf M, Siegenthaler W. Long-term follow-up after percutaneous transluminal coronary angioplasty. The early Zurich experience. *N Engl J Med* 1987;616:1127–32.

2 Gruntzig AR. Percutaneous transluminal coronary angioplasty 6 years experience. *Am Heart J* 1984;107:818–23.

3 Kaltenbach M, Kober G, Scherer D Mechanische Dilatation von Koronararterienstenosen (Transluminale Angioplastie). *Z Kardiol* 1980;69 1–10

4 Meyer J, Erbel R, Pop T, Rupprecht HJ. Derzeitiger Stand der intrakoronaren Ballondilatation. *Internist (Berl)* 1987;28.736–46.

5 Rupprecht HJ, Erbel R, Brennecke R, *et al.* Aktuelle Komplikationsrate der perkutanen transluminalen Koronar-angioplastie bei stabiler und unstabiler Angina. *Dtsch Med Wochenschr* 1988;113.409–13.

6 Ellis SG, Roubin GS, King SB, *et al.* In-hospital mortality after acute closure after coronary angioplasty: analysis of risk factors from 8207 procedures. *J Am Coll Cardiol* 1988;11:211–6.

7 Akins CW, Block PC. Surgical interventions for failed percutaneous transluminal coronary angioplasty. *Am J Cardiol* 1984;53:108C–11C

8 Erbel R, Schmitz HJ, Meyer J, *et al.* Percutaneous transluminal coronary angioplasty in patients with unstable angina. *Postgrad Med J* 1983;59:22–5.

9 Meyer J, Schmitz H, Erbel R, *et al.* Treatment of unstable angina pectoris with percutaneous transluminal coronary angioplasty. *Cathet Cardiovasc Diagn* 1981;7·361–71.

10 Vandormael MG, Deligonul U, Kern MJ, *et al.* Multilesion coronary angioplasty: clinical and angiographic follow-up. *J Am Coll Cardiol* 1987;10:246–52.

11 Cowley MJ, Dorros G, Kelsey SF, *et al.* Emergency coronary bypass surgery after coronary angioplasty: the National Heart, Lung, and Blood Institute's percutaneous transluminal coronary angioplasty registry experience. *Am J Cardiol* 1984;53:22C–6C

12 Shiu MF, Silverton NP, Oakley D, Cumberland D. Acute coronary occlusion during percutaneous transluminal coronary angioplasty. *Br Heart J* 1985;54 129–33.

13 Steffenino G, Meier B, Finci L, *et al.* Acute complications of

elective coronary angioplasty a review of 500 consecutive procedures. *Br Heart J* 1988;59:151–8.

14 Bredlau C, Roubin GS, Leimgruber PP, *et al*. In-hospital morbidity and mortality in patients undergoing elective coronary angioplasty. *Circulation* 1985;5:1044–52.

15 Leimgruber PP, Roubin GS, Anderson HV, *et al*. Influence of intimal dissection on restenosis after successful coronary angioplasty *Circulation* 1985,72:530–5.

16 Galan KM, Deligonul U, Kern MJ, *et al*. Increased frequency of restenosis in patients continuing to smoke cigarettes after percutaneous transluminal coronary angioplasty. *Am J Cardiol* 1988;61:260–3.

17 Kaltenbach M, Kober G, Schmidt-Moritz A, Scherer D. Rezidivhäufigkeit nach erfolgreicher transluminaler Koronarangioplastie. *Dtsch Med Wochenschr* 1983;108 1387–90.

18 Matthews BJ, Ewels CJ, Kent KM. Coronary dissection: a predictor of restenosis? *Am Heart J* 1988;115:547–54.

19 Sigwart U, Urban P, Golf S, *et al*. Emergency stenting for acute occlusion after coronary balloon angioplasty. *Circulation* 1988;78:1121–7.

20 Roubin GS, Douglas JS, Lembo NJ, *et al*. Intracoronary stenting for acute vessel closure following percutaneous transluminal coronary angioplasty (PTCA) [abstract] *Circulation* 1988;78(suppl II):II–406.

21 De Feyter PJ, DeScheerder I, van den Brand M, Laarman GJ, Suryapranata H, Serruys PW. Emergency stenting for refractory acute coronary artery occlusion during coronary angioplasty. *Am J Cardiol* 1990;66·1147–50.

22 Haude M, Erbel R, Straub U, Dietz U, Schatz R, Meyer J. Results on intracoronary stents for management of coronary dissection after balloon angioplasty. *Am J Cardiol* 1991;67:691–6.

23 Puel J, Rousseau H, Joffre F, *et al*. Intravascular stents to prevent restenosis after transluminal coronary angioplasty [abstract]. *Circulation* 1987;76(suppl IV) 27.

24 Puel J, Juilliere Y, Bertrand ME, *et al*. Early and late assessment of stenosis geometry after coronary arterial stenting. *Am J Cardiol* 1988;61:546–53

25 Schatz RA. A view of vascular stents. *Circulation* 1989;79: 445–57.

26 Roubin GS, King SB III, Douglas JS Jr, *et al* Intracoronary stenting during percutaneous transluminal coronary angioplasty *Circulation* 1990;81(suppl IV):IV92–100.

27 Erbel R, Schatz R, Diert U, *et al*. Percutaneous transluminal coronary stent implantation. *Z Kardiol* 1989;78 71–7.

28 Serruys PW, Strauss BH, Beatt KJ, *et al*. Angiographic follow-up after placement of a self-expanding coronary-artery stent. *N Engl J Med* 1991;324:13–7.

29 Schatz RA, Baim DS, Leon M, *et al*. Clinical experience with the Palmaz-Schatz™ coronary stent initial results of a multicenter study. *Circulation* 19??;83:148–61.

30 Sigwart U, Puel J, Mirkovitch V, *et al*. Intravascular stents to prevent occlusion and restenosis after transluminal angioplasty. *N Engl J Med* 1987;316:701–6.

31 Sigwart U, Imbert C, Essinger A, *et al*. One year percutaneous coronary stenting [abstract]. *Circulation* 1987, 76(suppl IV)·26.

32 Urban P, Sigwart U, Golf S, *et al*. Intravascular stenting for stenosis of aortocoronary venous bypass grafts. *J Am Coll Cardiol* 1989;13:1085–91.

33 Palmaz JC, Sibbitt RR, Tio FO, *et al* Expandable intraluminal vascular graft: a feasibility study. *Surgery* 1986; 99:199–205.

34 Palmaz JC, Kopp DT, Hayashi H, *et al*. Normal and stenotic renal arteries: experimental balloon-expandable intraluminal stenting. *Radiology* 1987;164:705–8

35 Palmaz JC, Windeler SA, Garcia F, *et al*. Atherosclerotic rabbit aortas expandable intraluminal grafting. *Radiology* 1986;160:723–6.

36 Schatz RA, Palmaz JC, Tio FO, *et al*. Balloon-expandable intracoronary stents in the adult dog. *Circulation* 1987; 76 450–7.

37 Schatz RA, Leon MB, Baim DS, *et al*. Balloon expandable intracoronary stents: initial results of a Multicenter Study [abstract] *Circulation* 1989;80(suppl II):174.

38 Brown BG, Bolson E, Frimer M, Dodge HT. Quantitative coronary arteriography. *Circulation* 1977,55·329–37.

39 Serruys PW, Beatt KJ, van der Giessen WJ. Stenting of coronary arteries. Are we the sorcerer's apprentice? *Eur Heart J* 1989;10:774–82.

40 Swars H, Hafner G, Erbel R, *et al*. Prothrombin fragment and thrombotic occlusion of coronary stents. *Lancet* 1991, 337 59.

41 Swars H, Hafner G, Erbel R, *et al*. Prothrombinfragment F1+2 predicts acute occlusion after intracoronary stenting [abstract]. *J Am Coll Cardiol* 1991;17:302A.

42 Rensing BJ, Serruys PW, Beatt KJ, *et al*. Densitometrically observed differences in elastic recoil of the three main coronary arteries after percutaneous transluminal coronary angioplasty [abstract]. *J Am Coll Cardiol* 1990; 15:42A.

43 Serruys PW, Juilliere Y, Bertrand ME, *et al*. Additional improvement of stenosis geometry in human coronary arteries by stenting after balloon dilatation. *Am J Cardiol* 1988,61:710–6G.

44 Beatt KJ, Bertrand M, Puel J, *et al*. Additional improvement in vessel lumen in the first 24 hours after stent implantation due to radial dilating force [abstract]. *J Am Coll Cardiol* 1989;13:224A.

Br Heart J 1991;66:346-50

Changes in Doppler indices of cardiac function during and after percutaneous transluminal coronary angioplasty

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Abstract

***Objective*—To assess the sensitivities of Doppler indices to changes in global cardiac function during and after controlled myocardial ischaemia induced by coronary angioplasty.**

***Design*—Continuous wave Doppler signals of aortic flow were recorded during coronary angioplasty. The following Doppler indices of cardiac function were measured before, during, and after balloon inflation: V (peak velocity), MA (mean acceleration), V^2/T (T = time from onset to peak ejection), and MD (minute distance corrected for baseline heart rate).**

***Setting*—A tertiary care cardiological unit in a university hospital.**

***Patients*—Sixteen patients undergoing coronary angioplasty of the left anterior descending coronary artery. Eight patients had multivessel disease.**

***Main outcome measures*—The primary outcome measures were planned before data collection began.**

***Results*—12 patients showed a significant fall of three or more Doppler indices from their baseline values during balloon inflation. This occurred in all patients with multivessel disease. The Doppler indices V^2 T, MD, V, and MA fell by 43·7%, 37·7%, 27·4%, and 23% respectively from their baseline values ($p < 0{\cdot}001$). The relative sensitivities of the Doppler indices to ischaemia were $V^2/T >$ MD ($p < 0{\cdot}02$), MD > ($p < 0{\cdot}001$), and V > MA ($p < 0{\cdot}01$). The impairment of global left ventricular function resulting from brief balloon inflation during single vessel angioplasty was reversible in all the patients.**

***Conclusions*—The Doppler indices V^2/T, MD, V, and MA are all sensitive, in order of magnitude, to falls in global cardiac function resulting from ischaemia. They may prove useful for assessing cardiac function during ischaemia in the clinical setting.**

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Balloon inflation during percutaneous transluminal coronary angioplasty produces considerable global and regional impairment of left ventricular function.[1-3] This impairment was reversible after brief periods of balloon occlusion in cases of angioplasty in single vessel disease.[3 4] A carefully controlled study has shown that after balloon deflation, indices of left ventricular systolic function return to normal within 40 s of reperfusion.[5] The changes in various Doppler indices of cardiac function during myocardial ischaemia have been studied in dogs[6] and in the exercising patient.[7 8] Doppler echocardiography has been successful in demonstrating changes in left ventricular function during angioplasty[9] but there has been little written about the relative sensitivities of Doppler indices in the angioplasty model of ischaemia. The purpose of this study was to assess the sensitivities of various Doppler indices to changes of cardiac function during and after coronary artery balloon occlusion.

Patients and methods

PATIENTS

We studied 16 patients (two women and 14 men), mean age 55 (range 40–70) years. Patients had stable limiting angina despite medical treatment. All the patients were in sinus rhythm and none had valve disease. Each patient gave informed verbal consent before the start of the study. Before enrolment patients were assessed for the presence of a suprasternal echocardiographic window that gave clean continuous Doppler signals of ascending aortic flow.

CORONARY ANATOMY

The 16 patients enrolled in the study required left anterior descending coronary artery angioplasty. The target stenoses had a mean value of 84% (range 75–90) and all allowed anterograde flow of contrast. Eight patients had single vessel disease and eight patients multivessel disease. In the multivessel disease group the diseased vessels associated with the target vessel had stenoses with a mean value of 75·8% (range 50–100) (table 1). None of the patients with single vessel disease had significant collateral supply to the target vessel. Of the eight patients with multivessel disease, four had ventriculographic evidence of pre-existing mild myocardial hypokinesia in the territory of the non-target vessel. These four patients had occlusions of their right coronary arteries, with three of them receiving a collateral supply (Rentrop grade 3–4[10]) from the target vessel.

There was no significant difference in the left ventricular ejection fractions between the groups of patients with single vessel and multivessel disease: mean values were

Table 1 Distribution of coronary artery disease in patients with multivessel disease undergoing angioplasty

Patients	*Target LAD (%)*	*RCA (%)*	*LCx (%)*	*Collaterals*
1	85	100	0	LAD → RCA (3)
2	95	100	50	0
3	90	50	0	0
4	80	100	50	LAD → RCA (4)
5	80	0	60	0
6	90	50	90	0
7	80	0	70	0
8	70	100	90	LAD → RCA (4)

LAD, left anterior descending coronary artery, LCx, circumflex coronary artery; RCA, right coronary artery; Rentrop gradings in parentheses

52% (range 40–65) and 69% (range 32–90) respectively.

PROTOCOL FOR PERCUTANEOUS TRANSLUMINAL CORONARY ANGIOPLASTY

All patients underwent angioplasty from the right femoral artery after insertion of an arterial sheath. A standard drug regimen was started at least 48 hours before the procedure. β-Blocking drugs were stopped and the patients were started on oral 300 mg aspirin, 20 mg nifedipine, and 10 mg isosorbide dinitrate. An infusion of isosorbide dinitrate (3 mg/h) was started two hours before and continued throughout the procedure and patients were fully heparinised. We used non-ionic contrast medium and a steerable guide wire angioplasty system.

DOPPLER SYSTEM

Ascending aortic blood velocity was evaluated transcutaneously from the suprasternal notch by a conventional continuous wave Doppler transmitter and a receiver operating at 2·0 MHz (Doptek decoder). The transducer was mounted on a spring loaded carriage held in a constant position by an adjustable frame. The position of the mechanical frame holding the transducer was set when a clean, continuous Doppler signal of maximum amplitude was obtained. Occasionally the transducer position was moved inadvertently by the patient but its position was rapidly corrected and a verbal note made into a roving microphone. This enabled us to avoid analysing unrepresentative Doppler signals recorded at the time of readjustment of the transducer. The received Doppler-shifted blood velocity signal was processed by Fourier analysis at a sampling rate of 5 ms and a spectral velocity envelope was displayed. Digital callipers allowed measurement of peak velocity to the nearest cm/s and time to the nearest 2·5 ms.

All signals obtained throughout the angioplasty procedure were recorded on to magnetic tape by an on line tape recording system. A roving microphone with an input into the recording system allowed events to be verbally recorded simultaneously with the recording of the Doppler signal.

DOPPLER MEASUREMENTS

Continuous wave Doppler recordings were obtained in supine patients at rest within the catheter laboratory throughout the angioplasty procedure. Digital callipers were used to measure peak velocity (V), time from onset of signal to peak velocity (T), heart rate, and stroke distance from the recorded signals. These measurements were made from five clear, nearly consecutive Doppler signals obtained at each of the following times: just before an inflation (baseline), at the end of a balloon inflation, and 120 s after balloon deflation. A mean of 8·7 consecutive signals (range 5–14) were measured on the initial baseline, and timing these as close to balloon inflation as possible allowed most of these measurements to be made at the time the deflated balloon catheter was across the lesion.

DATA ANALYSIS

We calculated V^2/T (a correlate of peak dP/dt) and MA (mean acceleration = V/T) from all measurements of V and T. The Doppler indices V, V^2/T, and MA were considered as indicators of the contractile state and minute distance corrected for baseline heart rate (MD) as an index of cardiac output. Corrected minute distance was calculated as stroke distance × baseline heart rate.

The standard deviation (SD) and coefficient of variation were calculated for the initial baseline values of heart rate, V, MA, MD, and V^2/T. We considered that subsequent changes in the magnitude of the Doppler indices that occured during balloon inflation were significant if the mean value decreased more than two SDs calculated from the initial baseline. Significant changes in cardiac function were deemed to occur in a patient during balloon inflation if three or more of the Doppler indices V, MA, V^2/T, and MD were significantly depressed.

For those patients showing a significant change in cardiac function during balloon inflation, the percentage change of a Doppler index from its baseline value was calculated as

$$\% \text{ change} = \frac{\text{baseline value} - \text{inflation value}}{\text{baseline value}} \times 100$$

Significant differences in the magnitude of change for each of these Doppler indices during a balloon inflation were analysed to determine the relative sensitivity of each Doppler index to the ischaemic insult. Analysis was by statistical comparison of the percentage change from the baseline of each Doppler index during the inflation period and at 120 s after the final inflation.

STATISTICAL ANALYSIS

The SD and coefficient of variation were calculated from the initial baseline values for each Doppler index. Subsequent changes in the indices were considered significant if they exceeded twice the SD. A two tailed *t* test was used to determine the significance of any change in the Doppler index. A paired *t* test was used to find the relative sensitivities of Doppler indices to changes in cardiac function. Statistics were performed on a Hewlett Packard HP-28S scientific calculator and with an Oxstat statistical package.

Results

Sixteen patients had a total of 33 inflations with

Table 2 Mean values of baseline Doppler indices for inflations in patients showing significant reductions in three Doppler indices during angioplasty

	1st Inflation					*2nd Inflation*					*3rd Inflation*					*4th Inflation*				
Patient	*HR*	*V*	*V^2/T*	*MA*	*MD*	*HR*	*V*	*V^2/T*	*MA*	*MD*	*HR*	*V*	*V^2/T*	*MA*	*MD*	*HR*	*V*	*V^2/T*	*MA*	*MD*
1	66	65·2	57·7	0·88	720						65	78	78	1	799					
2	61	71·8	103	1·43	660															
3	73	81·8	128	1·56	858															
4	58	62·8	61·7	0·98	621	66	72	86·4	1·2	818	60	71	85·9	1·2	786					
5	93	66·3	69·2	1·04	824	84	70	71	1·01	863										
6						89	43	23·7	0·55	746	92	45	27	0·6	925					
7	73	57·4	52	0·91	790	56	57	55	0·97	590	59	57	57	1·0	602					
8	91	50	29	0·58	830	95	56	41·8	0·75	874	92	48	34	0·71	811	90	50	34·2	0·69	754
9	54	88·5	121	1·39	696															
10	120	47·8	32·1	0·67	941	117	54	43·5	0·81	779										
11	85	67	93	1·39	574	64	79	138	1·75	629										
12	77	73	100	1·4	717															

HR, heart rate (beats/min), V, peak velocity (cm/s); T, time from onset to peak velocity (s); MD, minute distance corrected for baseline heart rate (cm); MA, mean acceleration ($\mathrm{cm/s^2} \times 10^3$). Patients 1–8, multivessel disease; patients 9–12, single vessel disease.

Table 3 Mean values of Doppler indices after 60 s inflation in patients showing significant reductions in three Doppler indices during angioplasty

	1st Inflation					*2nd Inflation*					*3rd Inflation*					*4th Inflation*				
Patient	*HR*	*V*	*V^2/T*	*MA*	*MD*	*HR*	*V*	*V^2/T*	*MA*	*MD*	*HR*	*V*	*V^2/T*	*MA*	*MD*	*HR*	*V*	*V^2/T*	*MA*	*MD*
1	67	66	61·5	0·91	780						65	51	34·3	0·67	490					
2	58	48	51	1·1	532															
3	63	64	64	1·0	397															
4	72	44	40	0·91	516	51	58	55·7	0·96	459	53	51·3	47·7	0·93	411					
5	92	62	56·5	0·91	795	84	58	48·1	0·82	755										
6						90	29	15·3	0·53	357	93	25	8·9	0·35	375					
7	61	44	32·8	0·75	416	57	39	28·2	0·72	335	60	41	28	0·68	400					
8	95	39	20·8	0·53	505	94	39	22·4	0·57	448	91	39	22	0·56	442	89	36	20·7	0·57	396
9	62	71·6	79	1·1	442															
10	121	29	12·9	0·45	531	104	25	11·6	0·46	362										
11	90	60	65	1·09	420	88	75	125	1·66	602										
12	69	56	56	1·0	631															

For explanations see footnote to table 2. Underlined figures indicate no significant reduction in values from baseline.

Table 4 Initial and final baseline mean values of Doppler indices in patients showing significant reductions in three Doppler indices during angioplasty

	Initial baseline					*Final baseline*				
Patient	*HR*	*V*	*V^2/T*	*MA*	*MD*	*HR*	*V*	*V^2/T*	*MA*	*MD*
1	66 (0) (0)	65·2 (3·2) (5)	57·7 (11·9) (20)	0·88 (0·14) (16)	720 (44·6) (6)	64	71	74·1	1·0	794
2	61 (1·13) (2)	71·8 (4·2) (6)	103 (14) (14)	1·43 (0·14) (10)	660 (100) (15)	56	74	96	1·3	509
3	73 (0·89)	81·8 (4·2) (5)	128 (21·6) (17)	1·56 (0·22) (14)	858 (89) (10)	52	112	208	1·9	642
4	58 (1·1) (2)	62·8 (1·5) (2)	61·7 (3·2) (5)	0·98 (0·04) (4)	621 (39) (6)	54	65	76·7	1·18	650
5	93 (0·6) (0·7)	66·3 (3·2) (5)	69·2 (9·7) (14)	1·04 (0·1) (10)	824 (54) (6)	84	68	68	1·0	819
6	90 (0·8) (0·9)	46·5 (2·9) (6)	27·8 (3·6) (13)	0·57 (0·07) (12)	710 (69) (10)	93	59	51·2	0·87	964
7	73 (7·6) (10)	57·4 (1·64) (3)	52 (4·6) (9)	0·91 (0·07) (8)	790 (91·2) (11)	61	56	52	0·93	618
8	91 (1·2) (1)	50 (2·4) (5)	29 (1·6) (6)	0·58 (0·03) (5)	830 (70) (8)	90	54	41·1	0·76	757
9	54 (0·7) (1)	88·5 (3·1) (4)	121 (8·9) (7)	1·39 (0·08) (6)	696 (44) (6)	57	89	121	1·36	481
10	120 (0·7) (0·6)	47·8 (2·95) (6)	32·1 (3·9) (12)	0·67 (0·05) (7)	941 (50) (5)	77	61	53·9	0·88	662
11	85 (1·9) (2)	67 (1·6) (2)	93 (8·4) (9)	1·4 (0·11) (8)	574 (44) (8)	78	90	147	1·7	890
12	77 (0·8) (1)	73 (4·3) (6)	100 (15·4) (15)	1·4 (0·18) (12)	717 (36) (5)	71	75	102	1·36	923

Initial baseline values and mean (SD) (coefficient of variation %). Final baseline values are means only. For other explanations see footnote to table 2.

a mean duration of 58·5 s per inflation. Fifteen inflations were performed in patients with single vessel disease and 18 inflations in patients with multivessel disease. Of the 16 patients undergoing angioplasty, 12 had significant falls ($p < 0{\cdot}001$) in three or more Doppler indices during one or more inflations. This occurred in all patients with multivessel disease (tables 2 and 3). We found no significant fall in Doppler indices when the first baseline was compared with the final baselines (table 4). In fact a significant increase ($p < 0{\cdot}001$) in two or more Doppler indices occurred in five patients (31%) at 120 s after the end of the final inflation. Three of these five patients had single vessel disease and two had multivessel disease. The relative sensitivities of the Doppler indices to changes in cardiac function were V^2/T, MD, V, and MA in order of magnitude. The significance levels in comparisons between V^2/T and MD, MD and V, and V and MA were $p < 0{\cdot}02$, $p < 0{\cdot}001$, and $p < 0{\cdot}01$ respectively (table 5).

Discussion

This is the first report of the relative sensitivities of Doppler indices to changes in global cardiac function that occur during controlled myocardial ischaemia produced by coronary angioplasty. Angioplasty produces a regional myocardial dysfunction in the mass of cardiac muscle supplied by the coronary artery undergoing balloon occlusion and, as in this study, past reports have also shown changes in

Table 5 Mean percentage change (SD) in Doppler indices of all patients having significant falls in three Doppler indices during balloon inflation and the relative sensitivities of these Doppler indices to change

	V^2/T	*MD*	*V*	*MA*
Percentage change	43 71 (12·6)	37·71 (12 8)	27 38 (10 3)	23 (9·93)
Sensitivity of index	V^2/T > MD p < 0 02	MD > V p < 0 001	V > MA p <.0 01	

For explanations see footnote to table 2.

global cardiac function during angioplasty.[1] The global left ventricular function that results from balloon occlusion represents an interplay between the reduced contractility of the ischaemic region of myocardium and the compensating hypercontractility of the non-ischaemic cardiac muscle. For this reason, while indices of global left ventricular function are not an accurate measure of regional myocardial dysfunction they do reflect overall haemodynamic cardiac performance in a patient during an ischaemic insult. Doppler echocardiography has advantages over other techniques for assessment of global left ventricular function during angioplasty; it is entirely non-invasive and allows continuous recording during and after each coronary occlusion. Cross sectional echocardiography successfully detects changes in left ventricular wall motion during balloon occlusion of the coronary artery.[2,4,11] Doppler echocardiography has been used to detect changes in left ventricular function during angioplasty in patients with poor collateral supply to their target vessel.[9] The disadvantages of Doppler echocardiography are variability of sampling axis, beat to beat variability in signal size, and interobserver variation. In our study we held the transducer sampling axis constant in relation to the patient by mounting the transducer on an adjustable metal frame. The same operator made measurements on all Doppler signals. We lessened the effect of beat to beat variability by averaging the measurements from five nearly consecutive Doppler signals recorded immediately before and at the end of the balloon inflation. It was difficult always to obtain consecutive signals of requisite quality but when this situation arose, we chose signals that were nearly consecutive. We considered a significant change in the value of a Doppler index to have occurred if the change in magnitude exceeded two SDs as calculated from the initial baseline.

In some patients the baseline values of the Doppler indices fluctuated substantially between inflations. This may have resulted from the smaller number of Doppler signals measured to obtain subsequent baseline values after the initial baseline recording. Therefore, in some cases, a decline in the values of Doppler indices from their baselines occurring during the balloon inflations after the first inflation may have under or overestimated the real magnitude of change in the Doppler index. This potential error has been reduced by ensuring that analysis of changes of individual Doppler indices was undertaken only in those patients who had a fall in three or more Doppler indices from their baseline. This improved the specificity when the changes that occurred within an individual Doppler index were analysed. Furthermore, all four Doppler indices fell in all inflations after the first, except for patient 6. We found a fall in MD during all inflations after the first in every patient. This more functional Doppler index of cardiac function was measured from reference points on the Doppler signal that were different from those used in measuring the other indices. This adds further support to the view that the significant falls from the baselines in Doppler indices, during balloon inflation, reflect real decreases in global cardiac function and that the apparent variability in the baseline values has not led us to false conclusions.

Doppler echocardiography to measure peak acceleration has been used to assess systolic function during angioplasty[9]; other studies have used the Doppler determined stroke integral index of mitral inflow[12] to investigate changes of cardiac function during angioplasty. The Doppler indices measured in this study are all indicators of global systolic left ventricular performance. Mean acceleration has been used effectively to assess changes in left ventricular contractility during myocardial ischaemia.[13] The index of peak velocity has been shown to be significantly reduced during ischaemia in animal[6,14] and clinical studies.[7,15] In a previous study we showed a good correlation between the index V^2/T and left ventricular peak dP/dt.[16] Doppler indices incorporating V were not significantly affected by heart rate.[6,13] Consequently we did not correct the Doppler indices V, MA, and V^2/T for heart rate in our study. Indices of cardiac output are affected by heart rate[6] and we corrected the minute distance accordingly. Although aortic pressure influences peak velocity,[6] previous careful study has not shown a significant change in mean aortic pressure during angioplasty.[3]

CHANGES IN DOPPLER INDICES OF LEFT VENTRICULAR FUNCTION DURING INFLATIONS

We defined changes in cardiac function during an inflation as significant if three or more Doppler indices decreased significantly from the baseline during that inflation. This definition increases the specificity of the positive results at the expense of the sensitivity. The finding of significant lowering of Doppler indices of cardiac function during balloon inflation accords with other reports that have shown decreases in Doppler indices and invasive indices of cardiac function.[1,3,9] In four patients with single vessel disease no significant fall in Doppler indices occurred during balloon occlusion. This may have been due to a compensating hypercontractility of the non-ischaemic myocardium or possibly recruitment of a collateral circulation.[10]

CHANGES OF DOPPLER INDICES OF LEFT VENTRICULAR FUNCTION AFTER INFLATION

We found no difference in the size of reductions in Doppler indices when we compared the first inflations with the last inflations and the first baselines with final baselines. This supports other studies that found a reversible impairment of left ventricular function after brief periods of ischaemia.[3 5] The conditions for the occurrence of a prolonged impairment of left ventricular function were optimal in the patients with multivessel disease and apparent lack of collateral supply to the target vessel. In particular the four patients with occluded right coronary arteries and mild myocardial hypokinesia would have been susceptible to prolonged impairment. Yet in our study this group of patients tolerated the after-effects of ischaemia as well as patients with single vessel disease. In 31% of patients there was a significant rise in the Doppler indices at 120 s after the final inflation. This increase in the value of Doppler indices occurred both in patients who did and those who did not show a fall in the Doppler indices of cardiac function during balloon inflation. It was also not related to the presence or absence of multivessel disease. This phenomenon has been described previously and hypercontractility of the reperfused myocardial wall[4] secondary to reactive hyperaemia in the target vessel[17] probably accounts for it.

SENSITIVITY OF DOPPLER INDICES TO CHANGES IN LEFT VENTRICULAR FUNCTION

The Doppler indices of contractility (V^2/T) and cardiac output (MD) were the most sensitive indicators of changing cardiac performance after the ischaemic insult of angioplasty. Both of these indices are more sensitive than V, which is known to be very sensitive to changes in left ventricular performance.[13] The indices V^2/T and MD are indicators of global cardiac contractility and cardiac output respectively. As such, they give a dynamic as well as functional assessment of global cardiac performance, much like the use of ejection fractions. The value of using Doppler indices of cardiac function lies in their ability to monitor non-invasively and continuously the changes in global cardiac performance that occur during and after myocardial ischaemia in an individual patient. They do not measure the regional myocardial dysfunction and are therefore not a useful measurement of the mass of ischaemic myocardium.

In conclusion, we used Doppler indices of aortic blood flow to measure changes in cardiac function during balloon occlusion of the coronary arteries. We have shown that the indices V^2/T, MD, V, and MA are sensitive to changes in global cardiac function during balloon occlusion. The more sensitive indices, V^2/T and MD, may be useful in clinical practice to assess global changes in cardiac performance.

1 Norell MS, Lyons JP, Gershlick AH, *et al.* Assessment of left ventricular performance during percutaneous transluminal coronary angioplasty: a study by intravenous digital subtraction ventriculography. *Br Heart J* 1988;59.419–28.

2 Hauser AM, Gangadharan V, Ramos RG, *et al.* Sequence of mechanical electrocardiographic and clinical effects of repeated coronary artery occlusion in human beings: echocardiographic observations during coronary angioplasty. *J Am Coll Cardiol* 1985;5:193–7.

3 Serruys PW, Wijns W, Van den Brand M, *et al.* Left ventricular performance, regional blood flow, wall motion and lactate metabolism during transluminal angioplasty. *Circulation* 1984;70:25–36.

4 Wohlgelernter D, Cleman M, Highman HA, *et al.* Regional myocardial dysfunction during coronary angioplasty. evaluation by 2-dimensional echocardiography and 12 lead electrocardiography. *J Am Coll Cardiol* 1986;7: 1245–54.

5 Carlson EB, Hinohara T, Morris KG. Recovery of systolic and diastolic left ventricular function after 60-second coronary arterial occlusion during percutaneous transluminal coronary angioplasty for angina pectoris. *Am J Cardiol* 1987;60.460–6.

6 Mathius DW, Wann LS, Sagar KB, *et al* The effect of myocardial ischaemia on Doppler echocardiographic indexes of left ventricular performance: influence of heart rate, aortic blood pressure and size of the ischaemic zone. *Am Heart J* 1988;116:953–60

7 Mehta N, Bennett D, Mannering D, *et al.* Usefulness of noninvasive Doppler measurement of ascending aortic blood velocity and acceleration in detecting impairment of the left ventricular functional response to exercise three weeks after acute myocardial infarction. *Am J Cardiol* 1986;58:879–84.

8 Harrison MR, Smith MD, Friedman JB, *et al.* Uses and limitations of exercise Doppler echocardiography in the diagnosis of ischaemic heart disease. *J Am Coll Cardiol* 1987;10:809–17.

9 Khaja F, Sabbah HN, Brymer JF, *et al.* Influence of coronary collaterals on left ventricular function in patients undergoing coronary angioplasty. *Am Heart J* 1988;116: 1174–80.

10 Rentrop KP, Cohen M, Blanke H, *et al.* Changes in collateral channel filling immediately after controlled coronary artery occlusion by an angioplasty balloon in human subjects. *J Am Coll Cardiol* 1985;5:587–92

11 Alam M, Khaja F, Brymer J, *et al.* Echocardiographic evaluation of left ventricular function during coronary artery angioplasty. *Am J Cardiol* 1986;57:20–5.

12 Labovitz AJ, Lewen MK, Kern M, *et al* Evaluation of left ventricular systolic and diastolic dysfunction during transient myocardial ischaemia produced by angioplasty. *J Am Coll Cardiol* 1987;10 748–55.

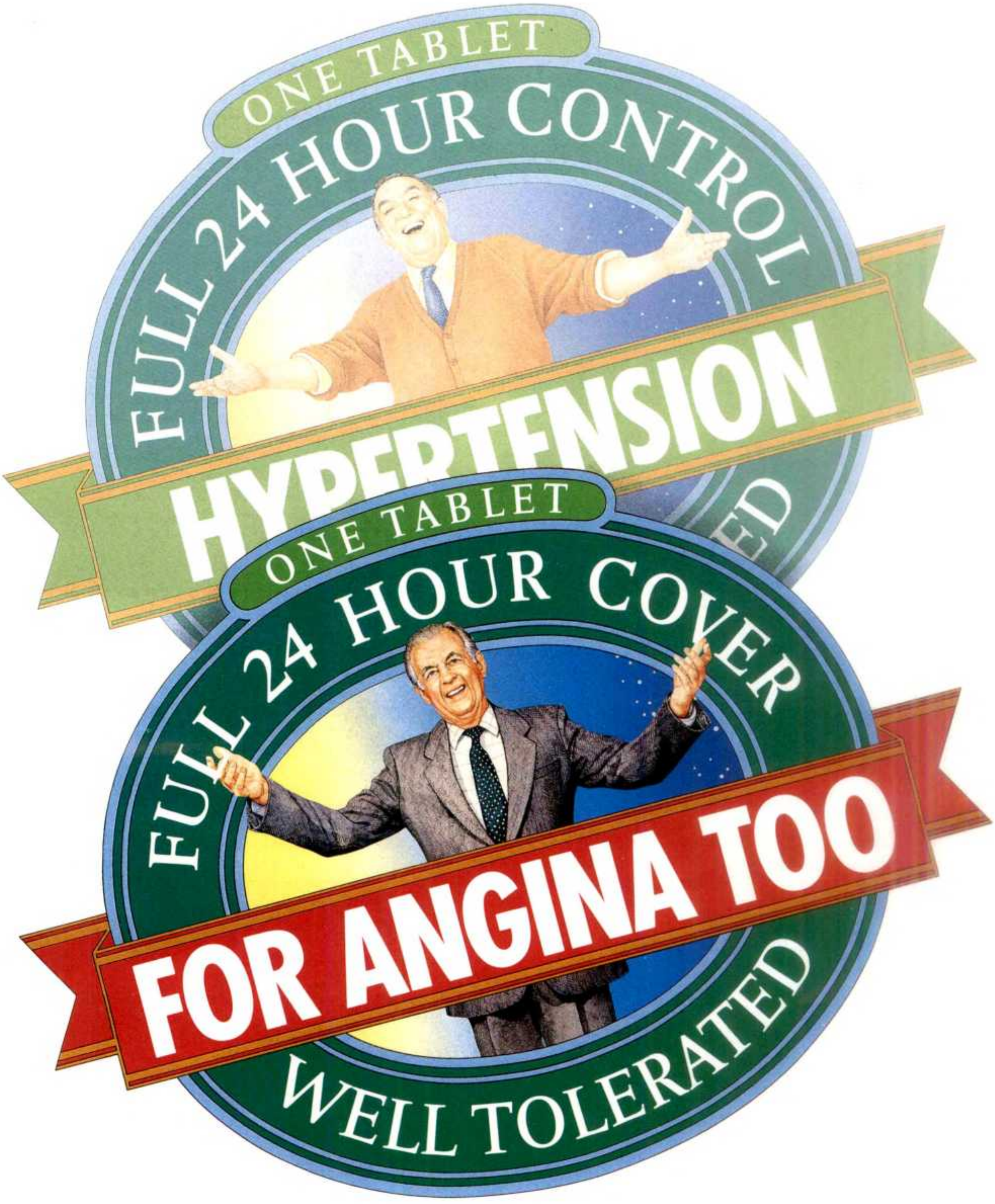
13 Wallmeyer K, Wann LS, Sagar KB, *et al.* The influence of preload and heart rate on Doppler echocardiographic indexes of left ventricular performance: comparison with invasive indexes in experimental preparation *Circulation* 1986;74:181–6.

14 Sabbah HN, Przybylski J, Albert DE, *et al.* Peak aortic blood acceleration reflects the extent of left ventricular ischaemic mass at risk. *Am Heart J* 1987;113:885–90.

15 Bryg RJ, Labovitz AJ, Mehdirah AA, *et al* Effect of coronary artery disease on Doppler-derived parameters of aortic flow during upright exercise. *Am J Cardiol* 1986;58:14–9.

16 Hunt AC, Perry RA, Seth A, *et al.* Non-invasive determination of dP/dt max by continuous wave Doppler echocardiography of aortic blood flow [abstract]. *J Am Coll Cardiol* 1989;13:60a.

17 Pagani M, Vatner SF, Baig H, *et al.* Initial myocardial adjustments to brief periods of ischaemia and reperfusion in the conscious dog. *Circ Res* 1978;43:83–92.



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References

1. Kjekshus, J., and Swedberg, K., *Amer. J Cardiol.*, 1989, **63**, 26D.
2. The SOLVD Investigators, *New Engl J Med*, 1991, **325**, 293.
3. Cohn, J. N., *et al.*, *New Engl J Med.*, 1991, **325**, 303.

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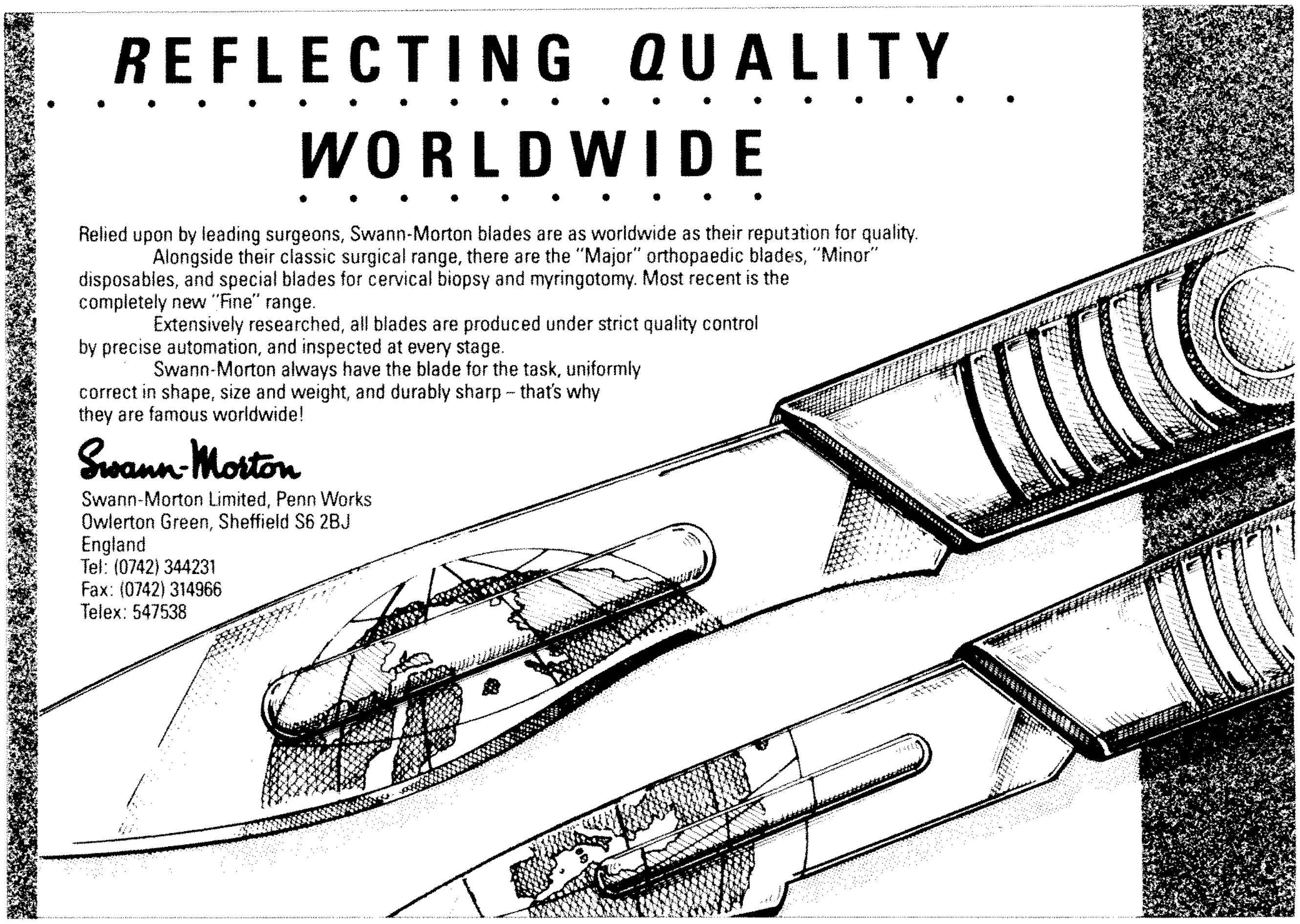

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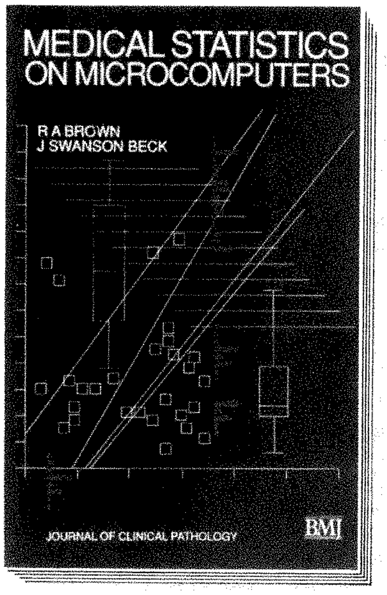
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von Willebrand factor in plasma: a novel risk factor for recurrent myocardial infarction and death

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Abstract

***Objective*—To evaluate as predictors of reinfarction and mortality tissue plasminogen activator antigen and activity before and after venous occlusion, plasminogen activator inhibitor, von Willebrand factor, and established risk factors.**

***Design*—Prospective study with a mean observation time of 4·9 years.**

***Setting*—Secondary referral centre, the Department of Internal Medicine, University Hospital of Umeå.**

***Patients*—123 consecutive survivors of myocardial infarction under the age of 70 years.**

***Main outcome measures*—Reinfarction and deaths from all causes.**

***Results*—23 patients died and 36 patients had at least one reinfarction. High concentrations of von Willebrand factor were independently associated with both reinfarction and mortality. A history of angina at entry into the study was also independently associated with reinfarction and mortality. Hypertension was independently associated with mortality but not with reinfarction. None of the fibrinolytic or lipid variables was associated with reinfarction or death.**

***Conclusion*—A high concentration of von Willebrand factor was a novel index of increased risk for reinfarction and mortality in survivors of myocardial infarction.**

Fibrinolysis was compromised in survivors of myocardial infarction by an increase in basal plasminogen activator inhibitor activity and reduced tissue plasminogen activator activity after the venous occlusion test.[1,2] Similar findings were reported in patients with angina.[3-5] In one report increased plasma plasminogen activator inhibitor activity was found to be an independent risk factor for reinfarction and cardiac death among young survivors of myocardial infarction,[6] and in another study tissue plasminogen activator antigen was significantly associated with cardiovascular events in patients with severe angina pectoris.[7] Low fibrinolytic activity has also been implicated as risk factor for restenosis after aortocoronary bypass surgery[8] and percutaneous transluminal coronary angioplasty.[9] The key fibrinolytic components—tissue plasminogen activator and plasminogen activator inhibitor—can be regarded as novel cardiovascular risk factors.

Plasma concentrations of von Willebrand factor are increased in disorders that affect the vascular system, such as systemic lupus erythematosus,[10] lupus anticoagulans,[11] thrombotic thrombocytopenic purpura,[12] pregnancy induced hypertension,[13] diabetes mellitus,[14] cerebrovascular disease,[15,16] and deep vein thrombosis.[15] Thus increased concentrations of von Willebrand factor may be important in the pathogenesis of cardiovascular disease.

In the present study, a long term follow up of our earlier cross sectional study[2] of survivors of myocardial infarction, we have compared tissue plasminogen activator, plasminogen activator inhibitor, and von Willebrand factor with previously established risk factors as predictors of reinfarction and mortality from all causes.

Patients and methods

PATIENTS

This study is based on 131 consecutive survivors of myocardial infarction aged less than 70 years who were followed up at the outpatient clinic of the Department of Internal Medicine, University Hospital of Umeå between 20 November 1982 and 28 November 1983.[2] Blood samples were collected three months after discharge from hospital. One patient died before sampling. We also excluded four patients with uncertain diagnosis, one patient in whom blood sampling failed, and two patients in whom clinical data were unaccessible. The remaining 123 patients, 95 men and 28 women, were included in the present study.

At infarction the mean (SD) age of the patients was 59·0 (8·0). Thirty six were smokers and 15 had diabetes mellitus. Table 1 shows the clinical and metabolic data.

FOLLOW UP STUDY PROTOCOL

In November 1988 the patients' records were searched for deaths and myocardial infarctions.

Table 1 Clinical characteristics of 123 survivors of myocardial infarction

Variable	*Number or mean (SD)*
Age (years) (mean (SD))	59 0 (8 0)
Hypertension (n)	37
Diabetes mellitus (n)	15
Smokers (n)	36
Previous angina pectoris (n)	66
Triglyceride (mmol/l) (mean (SD))	2 12 (1 01)
Cholesterol (mmol/l) (mean (SD))	7 00 (1 39)

Death certificates were obtained for all patients who had died. No patient was lost at follow-up. Myocardial infarction was diagnosed according to the World Health Organisation criteria.[17] The cause of death was taken from the death certificates. The term "any event" used in the statistical analyses indicates reinfarction or death.

BLOOD SAMPLING AND LABORATORY PROCEDURE

Three months after discharge from hospital blood samples were collected at rest and after 10 minutes venous occlusion (100 mm Hg for 10 minutes) and assayed for tissue plasminogen activator activity, tissue plasminogen activator antigen, and von Willebrand factor. Plasminogen activator inhibitor activity was measured only at rest. Assays of tissue plasminogen activator activity and plasminogen activator inhibitor activity were performed by a chromogenic substrate assay. Tissue plasminogen activator antigen and von Willebrand factor were measured by an ELISA. For further details see Nilsson and Johnson.[2]

STATISTICAL ANALYSIS

We used the Statistical Analysis System for statistics and analyses.[18] Standard summary statistics were used to summarise and illustrate the features of the data of interest.

To illustrate the relation between a possible prognostic factor and the incidence of reinfarction or mortality we divided baseline variables into quartiles, and calculated the incidence of events in each quartile per 100 patient years. These quartiles were *not* used to test relations. To test for a relation between a baseline variable and the incidence of reinfarction or mortality we used a Cox regression analysis.[19] Variables having a statistically significant relation with the incidence of events in a univariate analysis were further studied in a multivariate analysis. For each model we calculated a statistic (R) that measures the predictive ability of the model. $R^2 = (\text{model } \chi^2 - 2p)/-2L(0))$ where p is the number of variables in the model and L(0) is the log likelihood with no variables in the model—that is all regression coefficients set to 0. Individual R statistics, partial Rs, were also calculated for each variable in a model. These are defined as $R = (\text{MLE } \chi^2 - 2)/(-2L(0))^{\frac{1}{2}}$ and the sign of the corresponding regression coefficient is attached to R. R values are between − 1 and + 1 and provide a measure of the contribution of variables independent of the sample size. We used the Mann-Whitney test to compare groups with and without events. Two tailed tests were performed and p values below 0·05 were regarded as statistically significant.

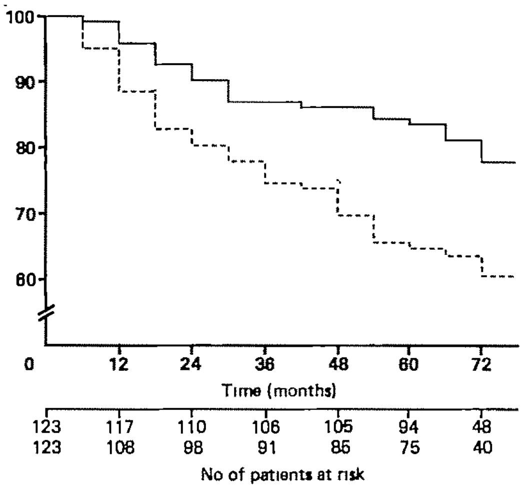

Figure 1 Life table showing the proportion of patients alive (solid line), remaining free of reinfarction (dotted line), or remaining free from any event (broken line). The numbers given underneath the graph show the number of patients at risk (uper row alive; lower row, free of reinfarction).

Results

The mean follow up time was 4·9 years. In the course of follow up 23 patients died (including four patients with fatal myocardial infarction) and 36 patients had at least one myocardial infarction (four fatal and 32 non-fatal). Figure 1 shows the life tables for the proportion remaining free of reinfarction, death, and any event. A 34 year old drug addict died from an overdose of methadone and one patient died from pulmonary thromboembolism. All the other 21 deaths were due to coronary heart disease.

The concentration of von Willebrand factor was significantly higher in the group with reinfarction and in the group of patients that died during follow up than in the groups without these events (table 2). There were no significant differences in the fibrinolytic vari-

Table 2 von Willebrand factor, fibrinolytic variables, and lipid variables according to the different outcome variables.

	Alive			*Dead*			*No reinfarction*			*Reinfarction*			*No event*			*Any event*		
Variable	*n*	*Mean*	*CI*	*n*	*Mean*	*CI*	*n*	*Mean*	*CI*	*n*	*Mean*	*CI*	*n*	*Mean*	*CI*	*n*	*Mean*	*CI*
vWf (% of normal)	100	143	131 to 155	23	177	157 to 196*	87	138	128 to 149	36	176	152 to 200*	78	134	123 to 144	45	176	156 to 196†
vWF occlusion (% of normal)	98	188	175 to 202	23	228	204 to 253*	86	185	172 to 199	35	222	196 to 247*	77	182	168 to 195	44	221	199 to 243*
tPA activity (U/ml)	100	0·10	0·08 to 0·12	23	0·13	0·09 to 0·17	87	0·10	0·08 to 0·12	36	0·11	0·09 to 0·13	78	0·10	0·08 to 0·12	45	0·12	0·08 to 0·16
tPA activity occlusion (U/ml)	98	2·0	1·4 to 2·6	23	2·0	1·2 to 2·8	86	2·0	1·4 to 2·6	35	2·0	1·2 to 2·8	77	2·0	1·4 to 2·6	44	2·1	1·4 to 2·8
tPA antigen (μg/l)	100	11·5	10·6 to 12·4	23	13·2	10·3 to 16·1	87	11·9	10·8 to 13·0	36	11·6	10·0 to 13·2	78	11·7	10·7 to 12·7	45	12·1	10·4 to 13·8
tPA antigen occlusion (μg/l)	98	36·4	31·5 to 41·3	23	40·6	27·7 to 53·5	86	37·6	32·3 to 42·9	35	36·3	26·7 to 45·9	77	36·8	31·4 to 42·2	44	38·0	29·3 to 46·7
PAI (U/ml)	100	10·0	8·7 to 11·3	23	9·7	6·8 to 12·6	87	10·5	9·1 to 11·9	36	8·8	6·8 to 10·8	78	10·4	9·0 to 11·8	45	9·1	7·1 to 11·1
Triglycerides (mmol/l)	87	2·0	1·8 to 2·2	18	2·5	1·8 to 3·2	77	2·1	1·9 to 2·3	28	2·1	1·8 to 2·5	70	2·1	1·9 to 2·3	35	2·2	1·8 to 2·6
Cholesterol (mmol/l)	89	7·0	6·7 to 7·3	18	7·3	6·7 to 7·9	78	7·0	6·7 to 7·3	29	6·9	6·4 to 7·4	71	7·0	6·7 to 7·3	36	6·9	6·5 to 7·3

*$p < 0·01$, †$p < 0·001$.

CI, 95% confidence interval, vWF, von Willebrand factor, tPA, tissue plasminogen activator, PAI, plasminogen activator inhibitor.

Table 3 Relation between risk factors and cardiovascular events (univariate Cox regression analysis)

	Mortality		*Reinfarction*		*Any event*	
Variable	*R*	*p*	*R*	*p*	*R*	*p*
Age		> 0·40		> 0·40		> 0·40
Sex		0·23		0·20		0·091
Smoking		> 0·40		> 0·40		> 0·40
Hypertension	0·13	0·018		> 0·40		0·18
Diabetes		> 0·40		> 0·40		> 0·40
Angina	0·17	0·005	0·15	0·0048	0·15	< 0·001
Triglyceride		0·090		> 0·40		> 0·40
Cholesterol		0·37		> 0·40		> 0·40
ASAT		> 0·40		> 0·40		> 0·40
vWF	0·13	0·016	0·19	0·0014	0·20	< 0·001
vWF occlusion	0·14	0·011	0·14	0·0038	0·14	0·0017
tPA activity		0·27		> 0·40		> 0·40
tPA activity occlusion		> 0·40		> 0·40		> 0·40
tPA-s		> 0·40		> 0·40		> 0·40
tPA-s occlusion		> 0·40		> 0·40		> 0·40
tPA antigen		0·10		> 0·40		> 0·40
tPA antigen occlusion		> 0·40		> 0·40		> 0·40
PAI		> 0·40		> 0·40		0·39

R, partial R statistic, see statistical methods; ASAT, aspartate aminotransferase, vWF, von Willebrand factor; tPA, tissue plasminogen activator, tPA-s, measurements in acidified blood; tPA activity, measurements in acidified plasma; PAI, plasminogen activator inhibitor.

ables between the group with events and the group without.

PROGNOSTIC FACTORS FOR REINFARCTION

Univariate Cox regression analyses showed that three of the variables studied were associated with reinfarction (table 3). Reinfarctions were more common in patients with previous angina and were positively associated with the concentration of von Willebrand factor both at rest and after venous occlusion (fig 2). The increase in the number of reinfarctions with increasing concentrations of von Willebrand, from the second to the fourth quartile accords with the close correlation between these two variables.

PROGNOSTIC FACTORS FOR MORTALITY

In univariate Cox regression analyses we found four of the studied variables to be associated with mortality (table 3). Of the primary risk factors for coronary heart disease, only hypertension was significantly associated with mortality; whereas age, sex, smoking, diabetes mellitus, serum cholesterol and triglyceride did not show a significant association. Those patients who had had angina at entry to the study were more likely to die. Figure 3 shows the number of deaths through quartiles one to four of the von Willebrand factor at rest and after venous occlusion. For both variables the number of deaths increased with increasing concentrations.

PROGNOSTIC FACTORS FOR ANY EVENT

In univariate Cox regression analyses we found three of the studied variables were associated with the occurrence of "any event" (table 3). The incidence of "any event" was more common in patients with previous angina, and was positively associated with von Willebrand factor at rest and after venous occlusion. Figure 4

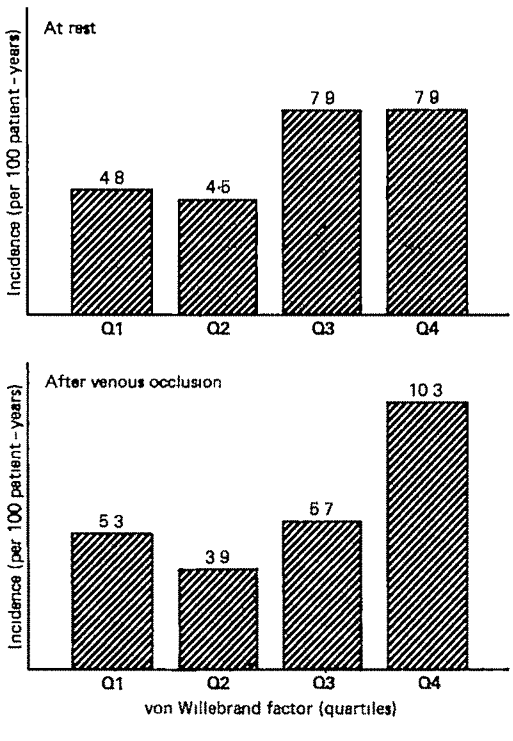

Figure 2 Incidence of reinfarction in relation to von Willebrand factor at rest and after venous occlusion.

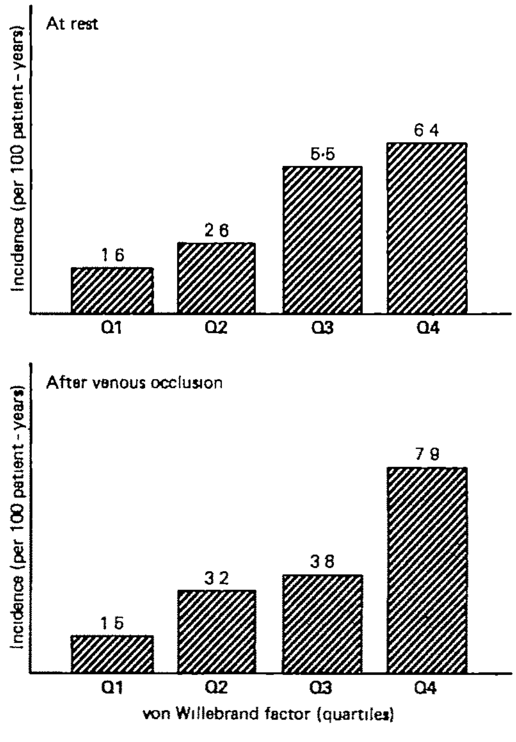

Figure 3 Incidence of mortality in relation to von Willebrand factor at rest and after venous occlusion.

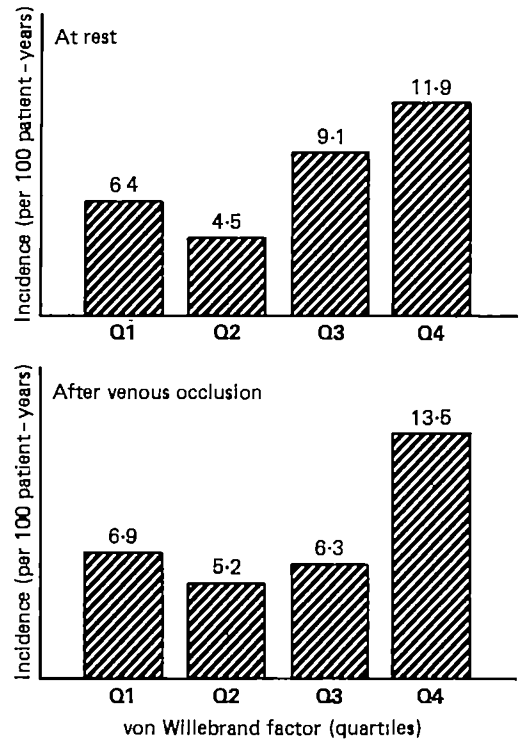

Figure 4 Incidence of any event in relation to von Willebrand factor at rest and after venous occlusion.

shows the number of any events through quartiles one to four of the von Willebrand factor at rest and after venous occlusion. Except for the first quartile both variables show an increasing number of any events with increasing concentrations.

MULTIVARIATE COX REGRESSION ANALYSES

All variables with $p < 0{\cdot}05$ in univariate regression (table 3) were included in multivariate analyses (except that the two von Willebrand factor variables, which are closely interrelated, were not included simultaneously), with reinfarction, mortality, and any event as dependent variables. The analyses were based on the 23 deaths and 99 living patients (35 patients with reinfarction and 87 patients without reinfarction; 45 with any event and 77 without any event) for all of whom data were complete. Previous angina and von Willebrand factor each made an independent contribution to the prediction of reinfarction and of any event (table 4). Hypertension, previous angina, and von Willebrand factor each made an independent contribution to the prediction of death (table 4).

Discussion

We found that high concentrations of von Willebrand factor, either at rest or after venous occlusion, were independently associated with reinfarction and mortality.

von Willebrand factor is synthetised by the vascular endothelium[20] and megakaryocytes.[21] It is an essential factor in primary haemostasis, and a hereditary deficiency of von Willebrand factor is associated with a bleeding disorder, von Willebrand disease. Increased concentrations of von Willebrand factor were associated with previous myocardial infarction in case-control studies,[22 23] and we found a tendency for patients to have higher concentrations than controls, but this difference did not reach statistical significance.[2] In an earlier study on survivors of myocardial infarction the patients who died within a year had significantly higher concentrations of von Willebrand factor.[24] In that study the blood samples were taken within the first week of admission and may thus have been affected by a non-specific acute phase reaction. There is also one study that showed no difference between survivors of myocardial infarction and controls,[1] but the patients in that study were younger, less than 45. In a longitudinal population study, there was a tendency for ischaemic heart disease events to increase with increasing concentrations of factor VIII (which correlates closely with the concentration of von Willebrand factor), but the association was not significant.[25]

Increased concentrations of von Willebrand factor have also been associated with clinical severity of angina,[26] deep venous thrombosis,[15] and ischaemic cerebrovascular disease.[15 16] These case-control studies tend to support the hypothesis that a high concentration of von Willebrand factor is an index of atherosclerosis or of increased risk of thromboembolic complications or both. Moreover, high concentrations of von Willebrand factor seem to be correlated with high concentrations of atherogenic growth factors.[27] In a previous prospective study high concentrations of von Willebrand factor were associated with an increased incidence of thromboembolic events. In that study, high concentrations of von Willebrand factor in preoperative samples were correlated with an increased risk of postoperative deep vein thrombosis after major abdominal surgery.[28]

von Willebrand factor has a role both in adhesion and aggregation of platelets and in coagulation. It is reasonable to assume that increased concentrations of von Willebrand factor may increase the risk of thrombus formation, at least in patients with pre-existing vascular wall disease such as coronary artery disease. On the other hand, endothelial damage in atherosclerotic coronary arteries may result

Table 4 Relation between risk factors, reinfarction, and cardiovascular mortality (multivariate Cox regression analysis)

	Reinfarction		*Mortality*		*Any event*	
Risk factor	*R*	*p*	*R*	*p*	*R*	*p*
Angina	0·13	0·0164	0·14	0·0150	0·10	0·0135
vWF at rest	0·11	0·0090	0·12	0·0280	0·15	< 0·001
Hypertension			0·14	0·0135		

vWF, von Willebrand factor; R, partial R statistic, see statistical methods.
Variables showing a significant ($p < 0{\cdot}05$) univariate association (table 2 and 3) were entered into the model.

in thrombin generation, causing increased secretion of von Willebrand factor. Thus our prospective data established that increased concentrations of von Willebrand factor are an indicator of increased risk, although the precise mechanism(s) for this are not yet known.

In our study there was no association between plasminogen activator inhibitor activity and reinfarction, death, or any event. This accords with our previous findings when we assessed plasminogen activator inhibitor as an index of risk for cardiovascular events in patients with severe angina pectoris and found that tissue plasminogen activator antigen concentration but not plasminogen activator inhibitor activity, was significantly associated with cardiovascular events.[7] High concentrations of plasminogen activator inhibitor, however, were independently related to reinfarction in young (< 45 years) survivors of myocardial infarction.[6]

Several of the established risk factors for myocardial infarction were not associated with reinfarction, death, or any event in the present study. This is probably because we did not study a large group of patients. This emphasises the potential value of von Willebrand factor measurements but does not mean that the other risk factors are unimportant.

Changes in the concentrations of both fibrinolytic variables and von Willebrand factor can be regarded as markers of endothelial cell dysfunction.[10 11 14 29] It may prove to be important to look for several markers of endothelial cell dysfunction when predicting cardiovascular events in patients with established coronary heart disease; and, moreover, the relative sensitivity of specific variables may vary with the population studied.

We thus regard a high concentration of von Willebrand factor as a novel index of increased risk for reinfarction and all-cause mortality in survivors of myocardial infarction.

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1 Hamsten A, Wiman B, De Faire U, Blomback M. Increased plasma levels of a rapid inhibitor of tissue plasminogen activator in young survivors of myocardial infarction. *N Engl J Med* 1985;313:1557–63
2 Nilsson TK, Johnson O. The extrinsic fibrinolytic system in survivors of myocardial infarction. *Thromb Res* 1987, 48:621–30.
3 Olofsson B-O, Dahlén G, Nilsson TK Evidence for increased levels of plasminogen activator inhibitor and tissue plasminogen activator in plasma of patients with angiographically verified coronary artery disease. *Eur Heart J* 1989;10:77–82.
4 Aznar J, Estellés A, Tormo G, *et al.* Plasminogen activator inhibitor activity and other fibrinolytic variables in patients with coronary artery disease *Br Heart J* 1988; 59.535–41.
5 Francis RB, Kawanishi D, Baruch T, Mahrer P, Rahimtoola S, Feinstein DI. Impaired fibrinolysis in coronary artery disease. *Am Heart J* 1988,115:776–80
6 Hamsten A, Walldius G, Blomback M, *et al* Plasminogen activator inhibitor in plasma· risk factor for recurrent myocardial infarction. *Lancet* 1987;ii·3–8
7 Jansson J-H, Nilsson TK, Olofsson B-O On the predictive value of plasminogen activator inhibitor and tissue plasminogen activator assays in patients with angiographically verified coronary artery disease. *Eur Heart J* 1991;12 157–61
8 Arnesen H, Semb G, Hol R, Karlsen H. Fibrinolytic capacity after venous stasis in patients undergoing aorto-coronary by-pass surgery. Relation to shunt occlusion *Scand J Haematol* 1983;30(suppl 39):43–6.
9 Kirschstein W, Simianer S, Dempfle CE, *et al.* Impaired fibrinolytic capacity and tissue plasminogen activator release in patients with restenosis after percutaneous transluminal coronary angioplasty (PTCA). *Thromb Haemost* 1989;62:772–5.
10 Angles-Cano E, Sultan Y, Clauvel JP. Predisposing factors to thrombosis in systemic lupus erythematosus. *J Lab Clin Med* 1979;94:313–23.
11 Nilsson TK, Lofvenberg E. Decreased fibrinolytic capacity and increased von Willebrand factor as indicators of endothelial cell dysfunction in patients with lupus anticoagulans *Clin Rheumatol* 1989,8:58–63.
12 Asada Y, Sumiyoshi A, Hayashi T, Suzumiya J, Kaketani K Immunohistochemistry of vascular lesion in thrombotic thrombocytopenic purpura, with special reference to factor VIII related antigen. *Thromb Res* 1985,38.469–79.
13 Brenner B, Zwang E, Bronshtein M, Seligsohn U. von Willebrand factor multimer patterns in pregnancy-induced hypertension. *Thromb Haemost* 1989;62:715–7
14 Greaves M, Pickering C, Knight G, *et al.* Changes in the factor VIII complex in diabetic ketoacidosis evidence of endothelial cell damage? *Diabetologia* 1987,30 160–5.
15 Wahlberg T, Blomback M, Övermark I. Blood coagulation studies in 45 patients with ischemic cerebrovascular disease and 44 patients with venous thromboembolic disease *Acta Med Scand* 1980;207:385–90.
16 Mettinger KL. A study of hemostasis in ischemic cerebrovascular disease I. Abnormalities in factor VIII and antithrombin. *Thromb Res* 1982;26:183–92.
17 Nomenclature and criteria for diagnosis of ischemic heart disease; report of the Joint International Society and Federation of Cardiology/World Health Organisation Task Force on Standardisation of Clinical Nomenclature. *Circulation* 1979,59:607–9.
18 Ray AA. *SAS user's guide: basics*. Cary, NC. SAS Institute, 1986.
19 Cox DR. Regression models and life tables (with discussion). *J R Stat Soc* 1972;34:187–220.
20 Jaffe EA, Hoyer LW, Nachman RL. Synthesis of von Willebrand factor by cultured human endothelial cells. *Proc Natl Acad Sci USA* 1974,71:1906–9.
21 Sporn LA, Chavin SI, Marder VJ, Wagner DD. Biosynthesis of von Willebrand protein by human megakaryocytes. *J Clin Invest* 1985;76:1102–6.
22 Schmitz-Huebner U, Thompson SG, Balleisen L, *et al.* Lack of association between haemostatic variables and the presence or the extent of coronary atherosclerosis. *Br Heart J* 1988;59:287–91.
23 Hamsten A, Blomback M, Wiman B, *et al.* Haemostatic function in myocardial infarction *Br Heart J* 1986;55: 58–66.
24 Haines AP, Howarth D, North WRS, *et al.* Haemostatic variables and the outcome of myocardial infarction *Thromb Haemost* 1983,50:800–3.
25 Meade TW, Brozovic M, Chakrabarti R. Haemostatic function and ischemic heart disease· principal results of the Northwick Park Heart study *Lancet* 1986,i:533–7.
26 Moisseev S. The role of hemostasis and rheologic properties of blood in stable and progressive exertion-induced stenocardia *Kardiologiia* 1988;28(11):67–71 [in Russian].
27 Nilsson J, Elgue G, Wallin M, Hamsten A, Blomback M. Correlation between plasma levels of growth factors and von Willebrand factor. *Thromb Res* 1989;54:125–32.
28 Nilsson T, Mellbring G, Hedner U. Relationship between factor XII, von Willebrand factor and postoperative deep vein thrombosis. *Acta Chir Scand* 1986;152.347–9.
29 Boneu B, Abbal M, Plante J, Bierme R Factor VIII complex and endothelial damage. *Lancet* 1975;i:1430.

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Increased concentrations of tumour necrosis factor in "cachectic" patients with severe chronic heart failure

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Abstract

***Objective*—To ascertain whether patients with cardiac failure and reduced body weight ("cardiac cachexia") have increased circulating concentrations of tumour necrosis factor (cachectin).**

***Design*—Patients with cardiac failure were prospectively identified as "cachectic" (body fat $<27\%$ in men and $<29\%$ in women measured by skinfold thickness callipers) or "non-cachectic". Tumour necrosis factor was assayed blind to patient group.**

***Setting*—Cardiology unit in a tertiary referral centre.**

***Patients*—26 consecutive patients (10 women) (mean age 61) admitted for investigation or treatment of chronic heart failure. All were in New York Heart Association class III or IV.**

***Results*—In nine of the 16 cachectic patients the concentration of tumour necrosis factor was increased (mean (SEM) 74 (20) pg/ml) compared with one of the 10 "non-cachectic" patients (22 pg/ml, $p < 0·001$). Patients with a raised circulating concentration of tumour necrosis factor weighed significantly less (55·6 (3·5) kg) than those in whom the concentration of tumour necrosis factor was normal (69·0 (4·1) kg) ($p = 0·02$).**

***Conclusions*—Circulating concentrations of tumour necrosis factor were increased in a significant proportion of patients with chronic heart failure and low body weight. Tumour necrosis factor stimulates catabolism experimentally and it may be a factor in the weight loss seen in patients with "cardiac cachexia".**

Some patients with chronic heart failure suffer generalised wasting referred to as "cardiac cachexia".[1] Inadequate nutritional intake is not thought to be the major aetiological factor.[1 2] Instead, it is suggested that cardiac cachexia is a catabolic state caused by the actions of a circulating factor.[1] The same factor is considered to be responsible for the cachexia characterising malignant conditions. Recently, a circulating polypeptide causing catabolism and, in laboratory animals, cachexia has been identified and labelled tumour necrosis factor or "cachectin".[3–5] We have measured tumour necrosis factor concentrations and body fat content in patients with chronic heart failure.

Patients and methods

PATIENT POPULATION AND SKINFOLD MEASUREMENT

Twenty six consecutive patients aged 31–81 (mean (SEM) 61 (2) years), 10 of whom were female, admitted for investigation or treatment of chronic heart failure were studied with ethical approval and after giving informed consent. Chronic heart failure was secondary to coronary artery disease in 17, valve disease in seven, idiopathic dilated cardiomyopathy in one, and congenital heart disease in one. All patients were in New York Heart Association clinical class III or IV and were being treated with diuretics; most were receiving an angiotensin converting enzyme inhibitor and digoxin. Patients with significant concomitant disease (for example, infection, renal failure, pulmonary disease, thyroid disease, malignancy, collagen-vascular disease) were not studied. Once treatment had been optimised, subcutaneous fat was measured—that is, in most cases immediately before discharge from hospital. We measured body fat content rather than body weight to avoid the potential complicating factor of residual fluid retention.[6] Using callipers, a single practised observer measured biceps, triceps, infrascapular, and suprailiac skinfold thickness in quadruplicate (skinfolds over the lower part of the body were again avoided because retained fluid collects in dependent regions). The percentage body fat content was derived from the sum of the mean of each of these measurements and standard tables.[7]

Patients were prospectively grouped as "cachectic" (males $<27\%$, females $<29\%$ body fat) and "non-cachectic" groups on the basis of body fat content; these percentage estimates were based on typical values for our non-chronic heart failure patients and published data from a local population.[7]

Venous blood was also collected from five healthy controls for measurement of tumour necrosis factor.

BLOOD COLLECTION AND TUMOUR NECROSIS FACTOR ASSAY

A 10 ml sample of antecubital venous blood was taken into chilled potassium EDTA tubes from supine, resting subjects. These samples were immediately centrifuged at 4°C and the separated plasma stored at −20°C until assay. All samples were assayed as a batch within two months of collection. Tumour necrosis factor was assayed without knowledge of which group patients belonged to, and whether the plasma was from a patient or

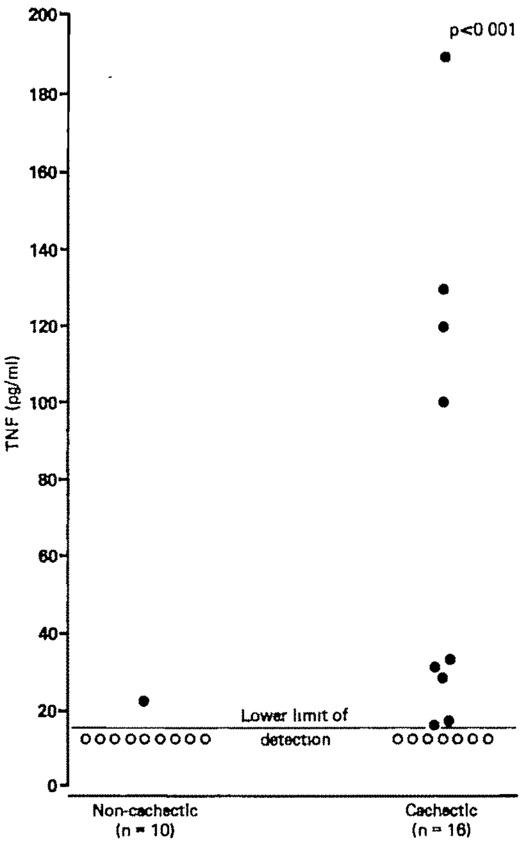

Figure 1 Plasma concentrations of tumour necrosis factor (pg/ml) in cachectic and non-cachectic patients with chronic heart failure. Lower limit of detection of assay (15 pg/ml); patients with concentrations below this are shown as open circles.

controls. Tumour necrosis factor was measured with a commercially available tumour necrosis factor α-radioimmunoassay (IRE-Medgenix, Brussels, Belgium).[8] Tumour necrosis factor should be undetectable (<15 pg/ml) in the plasma of healthy controls with this assay. The intra-assay and inter-assay coefficients of variation are 6·6% and 7·5%.

STATISTICAL ANALYSIS

The "non-cachectic" and "cachectic" groups of patients were compared by the χ^2 test. Subsequently the "normal" and "raised" TNF groups were compared by independent *t* tests. All values are given as mean (SEM).

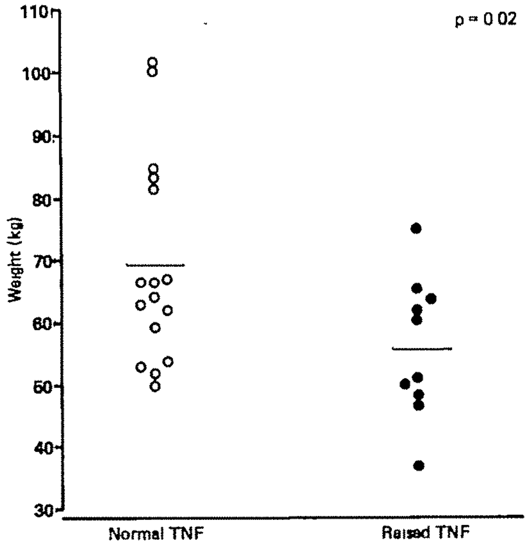

Figure 2 Body mass ("weight", kg) in patients with normal plasma concentrations of tumour necrosis factor (○) and those with raised concentrations (●).

Results

Sixteen patients (11 male) were "cachectic" (mean (SEM) body fat content 21 (1·2)%). Of these, nine (chronic heart failure due to coronary disease in seven, valve disease in one, and congenital heart disease in one) had mixed circulating concentration (>15 pg/ml) of tumour necrosis factor (fig 1). Ten patients were not cachectic (body fat 31 (1·0)%). Only one patient (with chronic heart failure due to coronary artery disease) in this second group had raised circulating concentration of tumour necrosis factor ($\chi^2 = 14{\cdot}8$, $p < 0{\cdot}001$).

Tumour necrosis factor was undetectable (<15 pg/ml) in frozen plasma from the five healthy controls.

Mean (SEM) body mass ("weight") was 69·0 (4·1) kg in patients with undetectable tumour necrosis factor and 55·6 (3·5) kg in those with raised concentrations (p = 0·02) (fig 2). Body mass index (mass in kg/height^2) was 24·8 (1·4) in patients with undetectable tumour necrosis factor and 20·3 (1·1) in those with raised concentrations (p = 0·02) (fig 3). Within the group of patients who were "cachectic" those with measurable tumour necrosis factor concentrations weighed 56·5 (3·8) kg and those without 66·0 (5·1).

Discussion

One of the many effects of tumour necrosis factor is to cause cachexia. Our findings showed that reduced body fat content in chronic heart failure was associated with raised concentrations of tumour necrosis factor and suggested that wasting in chronic heart failure may be due to the sustained effect of this polypeptide. Our results accord with those of a recent study in which patients with chronic heart failure were found to have higher concentrations of tumour necrosis factor, measured by bioassay, than controls. In that study the patients with the highest concentrations of tumour necrosis factor had lower body weights.[9] In the present study, a similar observation was made and body

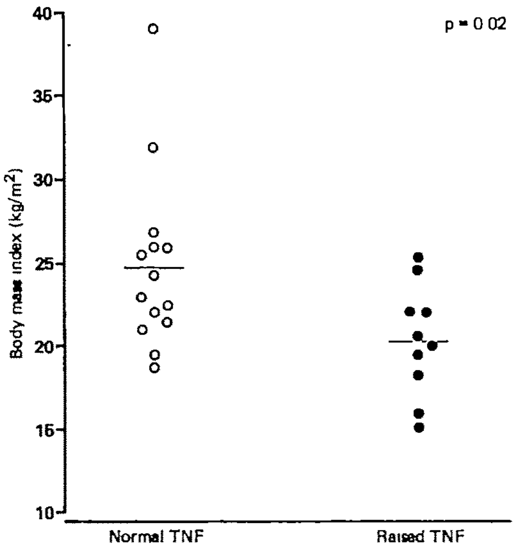

Figure 3 Body mass index (weight/height²) in patients with normal plasma concentrations of tumour necrosis factor (○) and those with raised concentrations (●).

mass index was also found to be decreased. Weight loss in other conditions, such as acquired immunodeficiency syndrome, chronic parasitic infection, and malignancy, has also been related to increased tumour necrosis factor concentrations.[10–13] Seven patients who were "cachectic", however, did not have raised concentrations of tumour necrosis factor. Why some wasted patients had high concentrations and others did not is unclear. Those "cachectic" patients who did have high tumour necrosis factor concentrations tended to weigh less than "cachectic" patients with normal concentrations, suggesting the circulating peptide is only increased in the most advanced states of cardiac cachexia syndrome. A similar pattern has been noted in other disease states. For example, in human immunodeficiency virus infection, only patients with full-blown acquired immunodeficiency syndrome have significantly raised concentrations of tumour necrosis factor (up to 200 pg/ml); those with acquired immunodeficiency syndrome related complex usually have normal cachectin concentrations.[13] This may suggest that enhanced tumour necrosis factor activity, undetectable by existing assays, is present in the early course of cachectic illnesses or that these wasting syndromes are multifactorial with other factors leading to weight loss in the early stages.

Cardiac cachexia is debilitating, leading eventually to severe skeletal muscle wasting and consequent immobility; it is also associated with a poor prognosis.[1] Recently, oxpentifylline has been reported to reduce the production of tumour necrosis factor in vitro and in vivo in healthy human volunteers.[14,15] This drug may offer the prospect of pharmacological intervention in cardiac cachexia. Fish oils too have been shown to suppress concentrations of tumour necrosis factor in humans, suggesting yet another therapeutic approach.[16] Corticosteroids, which suppress tumour necrosis factor production, or anti-tumour necrosis factor antibodies might also be of benefit in chronic heart failure patients with progressive wasting.[17,18]

Tumour necrosis factor has additional biological actions that may be disadvantageous in chronic heart failure. Tumour necrosis factor can promote intravascular coagulation, stimulate leucocyte adhesion and activation, and induce anaemia.[4,14,19] Tumour necrosis factor is also reported to depress myocardial contractility, alter muscle membrane potential, lower blood pressure, and precipitate pulmonary oedema.[20–22] Anti-tumour necrosis factor interventions might therefore have other potentially beneficial effects in chronic heart failure.

J McMurray is a British Heart Foundation Intermediate Research Fellow.

1 Ansari A Syndromes of cardiac cachexia and the cachectic heart: current perspective. *Prog Cardiovasc Dis* 1987;30·45–60.

2 Morrison WL, Edwards RHT Cardiac cachexia. *BMJ* 1991,302:301–2.

3 Beutler B, Cerami A. Cachectin and tumour necrosis factor as two sides of the same biological coin. *Nature* 1986, 320 584–8

4 Evans RD, Argiles JM, Williamson DH. Metabolic effects of tumour necrosis factor—α (cachectin) and interleukin-1. *Clin Sci* 1989;77 357–64.

5 Starnes HF, Warren RS, Jeevanandam M, Gabiolove JL, Larchian W, Oettgen HF, *et al.* Tumour necrosis factor and the acute metabolic response to tissue injury in man. *J Clin Invest* 1988;82:1321–5.

6 Blackburn GL, Harvey KB Nutritional assessment as a routine in clinical medicine. *Postgrad Med* 1982;71 46–63.

7 Durnin JVGA, Womersley J. Bodyfat assessed from total body density and its estimation from skinfold thickness: measurements on 481 men and women aged from 16–72 years. *Br J Nutr* 1974,32:77–97.

8 Leroux-Roels G, Offner F, Phillippe J, Vermuelen A Influence of blood collecting systems on concentrations of tumour necrosis factor in serum and plasma. *Clin Chem* 1988;11 2373–4

9 Levine B, Kalman J, Mayer L, Fillit HM, Packer M. Elevated circulating levels of tumour necrosis factor in severe chronic heart failure *N Engl J Med* 1990;323·236–41.

10 Kern P, Hemmer CJ, van Damme J, Gruss HJ, Dietrich M. Elevated tumor necrosis factor alpha and interleukin-G serum levels as markers for complicated *Plasmodium falciparum* malaria *Am J Med* 1986;2:1364–5.

11 Balkwill F, Burke F, Talbot D, Tavernier J, Osborne R, Naylor S, *et al.* Evidence for tumour necrosis factor/cachectin production in cancer. *Lancet* 1987;ii·1229–32.

12 Scuderi P, Lam KS, Ryan KJ, Petersen E, Sterling KE, Finley PR, *et al.* Raised serum levels of tumour necrosis factor in parasitic infections. *Lancet* 1986;ii·1364–5.

13 Lahdevirta J, Maury CPJ, Teppo A-M, Repo H. Elevated levels of circulating cachectin/tumour necrosis factor in patients with acquired immunodeficiency syndrome. *Am J Med* 1988;85:289–91.

14 Zabel P, Walter DT, Schonharting MM, Schade UF. Oxpentifylline in endotoxaemia *Lancet* 1989;ii.1474–7.

15 Waage A, Sorensen M, Stordal B. Differential effect of oxpentifylline on tumour necrosis factor and interleukin 6 production. *Lancet* 1990;i.542–3

16 Endres S, Ghorbani R, Kelley VE, Georgilis K, Lonnemann G, van der Meer JW, *et al.* The effect of dietary supplementation with n-3 polyunsaturated fatty acids on the synthesis of interleukin -1 and tumor necrosis factor by mono nuclear cells. *N Engl J Med* 1989;320:265–71

17 Tracey KJ, Vlassara H, Cerami A Cachectin/Tumour necrosis factor. *Lancet* 1989;i:1122–6.

18 Beutler B, Milsark IW, Cerami A. Passive immunisation against cachectin/tumour necrosis factor protects mice from the lethal effect of endotoxin *Science* 1985;229. 869–71.

19 van der Poll T, Buller HR, tenCate H, Wortel CH, Bauer KA, van Deventer SJH, *et al.* Activation of coagulation after administration of tumour necrosis factor to normal subjects. *N Engl J Med* 1990,322:1622–7.

20 Hocking DC, Phillips PG, Ferro TJ, Johnson A. Mechanisms of pulmonary oedema induced by tumour necrosis factor-α. *Circ Res* 1990;67:68–77.

21 Tracey KJ, Lowry SF, Beutler B, Cerami A, Albert JD, Shires GT. Cachectin/tumour necrosis factor mediates changes of skeletal muscle plasma membrane potential. *J Exp Med* 1986;164:1368–73.

22 Cunnion RE, Parillo JE. Myocardial dysfunction in sepsis. *Chest* 1989,95:941–5.

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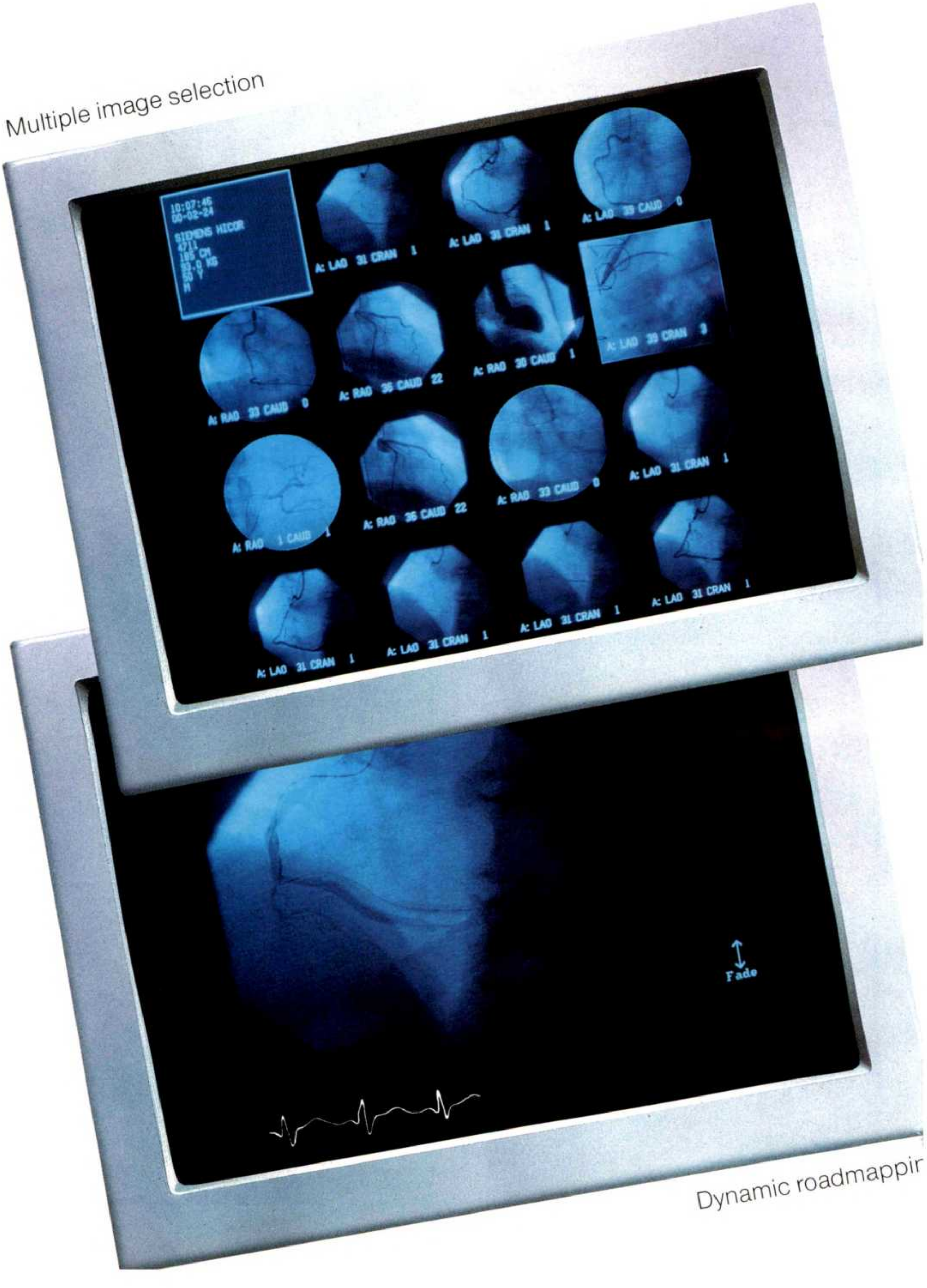

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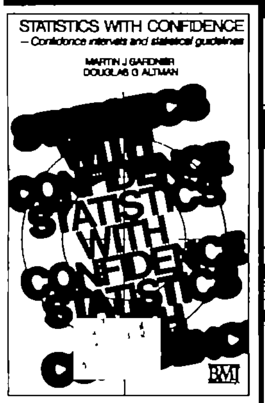
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Br Heart J 1991;66:359–63

Estimating the size of myocardial infarction by magnetic resonance imaging

L W Turnbull, J P Ridgway, J J Nicoll, D Bell, J J K Best, A L Muir

Abstract

***Objective*—To develop a method to measure myocardial infarct size by magnetic resonance imaging and to compare the results with pyrophosphate scanning by single photon emission computed tomography.**

***Design*—All patients underwent magnetic resonance imaging and pyrophosphate scanning 5–7 days after the onset of symptoms. Both measurements of infarct size were compared with the release of creatine kinase MB and with ventricular performance estimated by radionuclide ventriculography.**

***Patients*—19 patients (age 40–68 years) who had sustained their first uncomplicated myocardial infarction and who had not been treated with thrombolytic therapy.**

***Results*—The site of infarction was clearly shown by both imaging techniques and was identical in each patient. The volume of infarcted tissue measured by magnetic resonance imaging agreed well with the infarct size measured by single photon emission tomography (mean difference 2·7 cm^3). Correlations of both imaging techniques with the release of creatine kinase MB were best when total release rather than peak release was used. Both imaging techniques correlated closely with the subsequent ventricular performance.**

***Conclusions*—Magnetic resonance imaging after acute infarction allows measurement of infarct size and this may prove useful in assessing new treatments designed to salvage myocardium.**

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Prognosis after acute myocardial infarction depends on the extent of myocardial damage and on residual left ventricular function. Salvage of acutely ischaemic but reversibly damaged myocardium is widely accepted to be responsible for the preservation of ventricular function and for improved survival after thrombolytic therapy.[1,2] However, there are discrepancies between survival after reperfusion and residual left ventricular function,[3] and it has been suggested that the beneficial effects of thrombolysis may be more complex than a simple reduction in infarct size. Currently, ventricular function is used as an indirect indicator of the mass of ventricle infarcted, but in patients with previous infarction this relation is distorted. More direct measurements of infarct size are required to clarify the effects of intervention.

Of the other standard techniques (including ST segment and R wave mapping, cardiac enzyme release, and echocardiography) only radionuclide imaging with infarct avid agents attempts directly to measure the mass of damaged myocardium. Recent reports suggest that magnetic resonance imaging may offer considerable advantages for direct measurement of infarct size.[4,5] Studies in both animals and humans have shown that infarcted muscle can be recognised on gated magnetic resonance images and we showed that there is an increase in the relaxation parameter, T1, in patients after acute infarction.[6] In animal studies there was a close relation between infarct size measured from areas of increased pixel intensity on magnetic resonance images and anatomical estimates of myocardial injury identified histochemically.[7]

To extend these observations to humans we examined myocardial infarct size with a low field magnetic resonance imaging system and compared the estimated injury with single photon emission tomographic images of 99m-technetium pyrophosphate uptake, with release of the enzyme creatine kinase MB, and with residual left ventricular function measured by radionuclide ventriculography.

Patients and methods

PATIENTS

We studied 19 patients (14 men and five women) who had sustained their first myocardial infarction and who had not been treated with thrombolytic drugs. Myocardial infarction was diagnosed on the basis of history and typical electrocardiographic or cardiac enzyme changes or both. At the time of the examination all patients were clinically stable with no evidence of either acute pulmonary oedema or low output cardiogenic shock. The patients were all in sinus rhythm and gave informed consent before entering the study. None of the patients gave a history of previous cardiac disease or of other chronic medical conditions

MAGNETIC RESONANCE IMAGING

Technique

In all patients magnetic resonance imaging was carried out five to seven days after the onset of chest pain with a low field system (M & D Technology) operating at 0·08 T. Patients with either temporary or permanent cardiac pacemakers, prosthetic heart valves, or previous intracranial surgery had already been

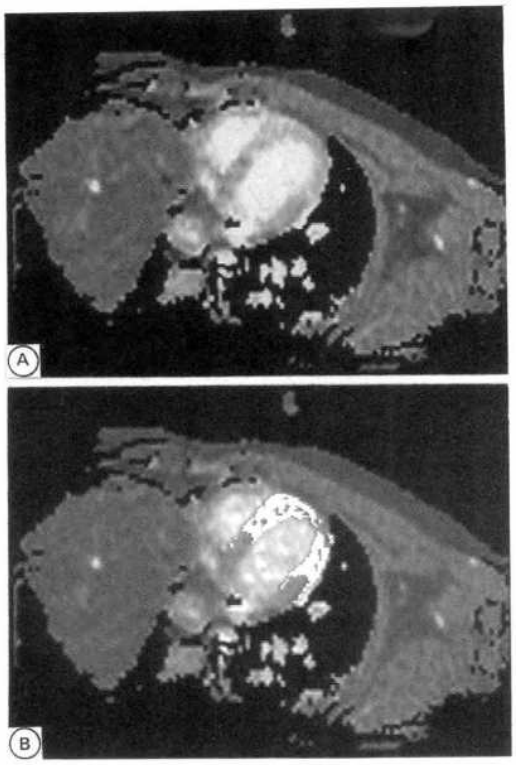

Figure 1 (A) T1 map of an angied transverse image obtained through the ventricles showing a large semicircular area of reduced signal intensity involving the interventricular septum and adjacent anterior left ventricular wall secondary to infarction. (B) Areas within the myocardium with a T1 value two standard deviations or more above the mean T1 value for normal myocardium are shown in white.

excluded from the study. Scout images were initially carried out in the coronal plane to visualise the long axis of the ventricles. These images were obtained with a field of view of 384 mm, a matrix of 128 × 64, a short repetition time (TR) of 240 ms, and a field echo time of 22 ms. Four slices were obtained with a 16 mm slice thickness and separation. From these images, short axis views of the ventricular chambers were aligned. We used a cardiac gating technique with carbon fibre electrodes (Abingdon Instruments, Abingdon, Oxford) placed on the left anterolateral and the right parasternal chest wall.[8] The downslope of the electrocardiographic T wave was used to synchronise data acquisition during end systole at approximately 110 ms after the upstroke of the T wave. An interleaved saturation recovery-inversion recovery pulse sequence was used with a TI of 42 ms and a variable TR, depending on the RR interval. Eight to 10 slices (12 mm thick) were acquired as four acquisitions to obtain multiple images from below the cardiac apex to the level of the aortic arch. Two slices with a 42 ms time separation were obtained with each acquisition which consisted of two averages of 64 phase encoding steps and 128 frequency encoding steps resulting in a pixel size of 3 × 6 mm. These data were interpolated to a 128 × 128 matrix (3 × 3 mm) and smoothed on the final display monitor for image analysis.

Analysis

The calculated T1 map showed good contrast between normal myocardium, ischaemic myocardium, and chamber contents, and was used to define the myocardial border (fig 1A). The outlines of the endocardial and epicardial interfaces of the left ventricle, including the interventricular septum, were defined interactively by using image analysis software to draw an irregular region of interest. Owing to partial volume effects from pericardial fat the T1 values of the extreme apical segment were frequently higher than those of the normal myocardium, and these images were therefore excluded from analysis. The T1 calculations[9] were based on a look-up table that was generated from the saturation recovery and "difference" image signals when a repetition time of 1000 ms was assumed. However, because it was shown from phantom experiments that our measurements of T1 values, which are based on these look-up tables, varied considerably with heart rate it was necessary to calculate an upper limit of normal for each individual patient. This was done by taking the mean T1 value plus two standard deviations from regions of a fixed size (approximately $2\ cm^3$) placed within normal myocardium on all the slices that included the left ventricle. These regions of interest were as remote as possible from the areas of increased signal and were retrospectively confirmed to be separate from regions of increased pyrophosphate uptake. An average T1 value was obtained for all the slices measured. Regions within the myocardium with a T1 value greater than this limit were then generated by the computer (fig 1B) and their areas measured. These values were multiplied by the slice thickness to obtain the volume of the infarcted myocardium on each slice, and then these volumes were summed to obtain the total volume of infarcted myocardium.

REPRODUCIBILITY

The reproducibility of the technique was affected by the measurement of both the mean and standard deviation of normal myocardium and by identification of the endocardial and epicardial borders of the left ventricle. To determine the intra and inter observer variability two independent observers performed measurements on the same four patient examinations on three separate occasions.

The volume of infarcted myocardial tissue varied by 10·1% between observers and the intra observer variability was 6·8 and 10·4%. This variation was primarily attributable to the difference of 8·8% between the two measurements of the upper threshold limit for normal myocardium (mean (2 SD)).

99M-TECHNETIUM PYROPHOSPHATE SCANNING

Radioisotope scanning with 99m-technetium pyrophosphate was performed with a Maxi-Camera 400AT Gamma Camera equipped with a low energy, general purpose, parallel hole collimator (International General Electric) and a MicroDelta Plus computer system (Siemens Gammasonics). Patients were imaged between 24 and 36 hours after admission to hospital and two hours after administration of 600 MBq 99m-technetium pyrophosphate. Patients were positioned supine with both arms beside the head. Single photon emission tomography was performed with a set of sixty four, 64 × 64 images taken over a 360° arc with the radius of rotation selected to minimise the distance from the detector to the chest wall. Each image was collected for a preset time of 10 seconds and, in addition to the "auto-tune" facility, the camera was further corrected for uniformity (using a 30 million count ^{99m}Tc flood) and for the centre of rotation. Transverse images, one pixel thick, were reconstructed "on line" with a Butterworth filter of order 5 and a cut-off frequency of 0·5 Nyquist. The myocardial uptake of pyrophosphate was determined from the transverse images by a simple three dimensional thresholding procedure operating at 65% of the peak voxel value within the infarct volume. The threshold value of 65% has been shown[10] from phantom studies to be the optimal value. The peak value in the volume of interest was found after each transverse slice had been smoothed twice by a nine point filter. Myocardial uptake was analysed by drawing a cuboid region of interest around the heart and counting the number of voxels $>65\%$ of the peak value within that volume (fig 2). The number of infarct voxels was then summed and the size of infarction determined by multiplying by the voxel size (0·24 cm^3/voxel).

Before we calculated infarct volume we reviewed each transverse image, and if necessary, modified the region of interest to exclude areas of non-cardiac uptake such as the sternum or ribs.

SERUM CREATINE KINASE MB

Serum creatine kinase MB was measured by an optimised kinetic spectrophotometer assay. In 11 of the 19 patients, 4–8 blood samples were obtained from eight to 48 hours after the onset of symptoms. This allowed calculation of the total creatine kinase released. In the remaining eight patients only three blood samples were obtained and we used the highest value to express a "peak" creatine kinase release. Both the total and the peak creatine kinase release were used in our correlations.

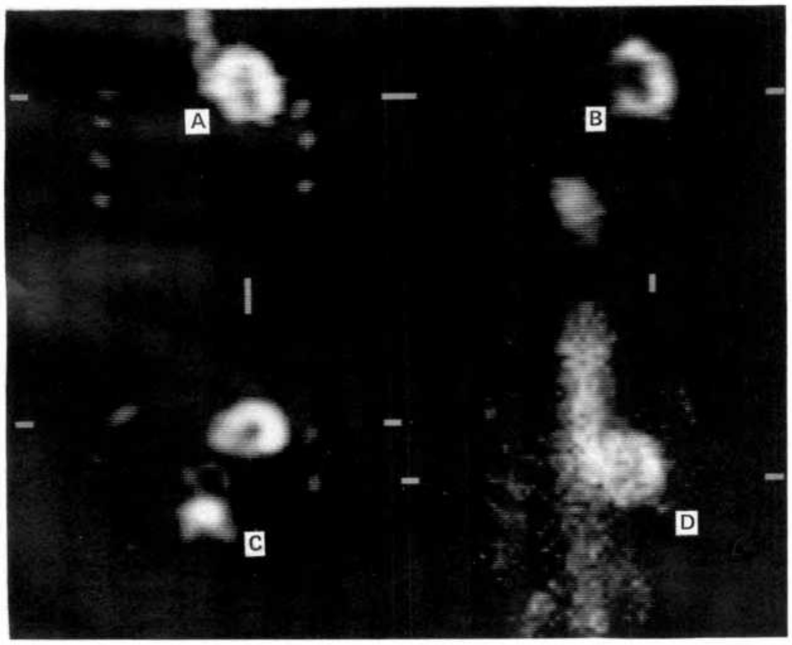

Figure 2 Single photon emission tomographic images of ^{99m}Tc-pyrophosphate uptake in the myocardium of the same patient as fig 1. A and B show an extensive anterior infarction. (A) coronal section; (B) sagittal section; (C) transverse section; (D) scout image roughly equating to a planar anterior view.

RADIONUCLIDE VENTRICULOGRAPHY

This was carried out on the day before discharge from hospital (mean 7 days), when the patient was clinically and radiologically clear of heart failure. All the patients were studied in the supine position and cardiac imaging was performed in approximately a 30° left anterior oblique projection with a 10° caudal tilt. The precise angle was chosen to optimise the separation of the ventricles. After injection of 700 MBq ^{99m}Tc human serum albumin, imaging was carried out with a Siemens low energy mobile gamma camera and the data were collected by a Micro Delta computer. The ejection fraction was calculated by a gated blood pool technique.[11]

STATISTICAL ANALYSIS

Statistical analysis was performed with the SPSS/PC+ computer programme.

Results

The location of the infarct was clearly demonstrated and was identical by both pyrophosphate scanning and magnetic resonance imaging in 17 of the 19 patients. No abnormality was shown by either imaging technique in one patient, while in a second pyrophosphate imaging showed only a very small area of increased uptake anteriorly, but magnetic resonance imaging failed to demonstrate any abnormality. In the first of these two patients the electrocardiogram was normal and in the second it was indeterminate owing to the presence of left bundle branch block. Both patients showed only a minor rise in the peak serum creatine kinase MB values of 172 and 522 U/l respectively.

We compared the myocardial infarct size measured by pyrophosphate scanning and magnetic resonance imaging by plotting the difference between the two values against the mean infarct size obtained from both methods[12] (fig 3). This showed a mean difference of 2·7 cm^3 (magnetic resonance infarct size minus pyrophosphate infarct size), while the standard deviation of the difference was 9·9 cm^3. The limits of agreement were $-$ 22·5 and 17·1 cm^3 and the standard error of the mean was 2·27 cm^3. Hence the 95% confidence interval for the lower limit of agreement was $-$30·8 to $-$14·3 cm^3, while for the upper limit of agreement the 95% confidence interval was 8·9 to 25·4 cm^3. These intervals showed moderately good agreement between the two methods, with reasonable consistency over the range of values encountered, although discrepancies were noted with infarct sizes >80 cm^3.

The table shows the correlations between infarct size, creatine kinase MB release, and left ventricular ejection fraction. The creatine kinase MB release curves could be calculated in only 11 patients, but there was a good correlation between the peak and total creatine kinase

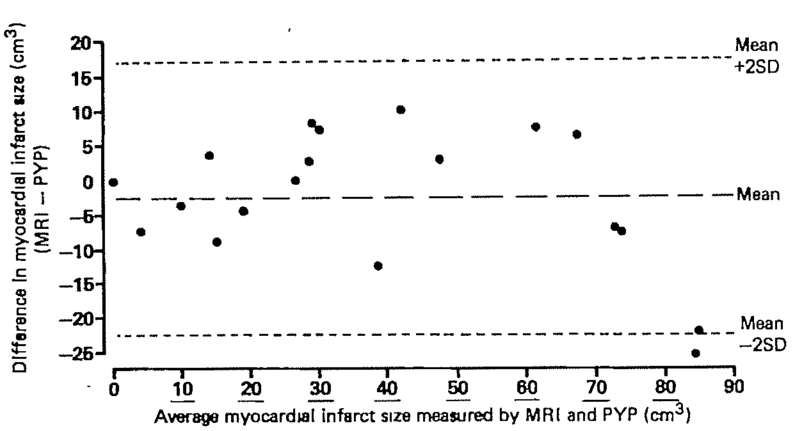

Figure 3 Difference in myocardial infarct size between magnetic resonance imaging (MRI) and ^{99m}Tc-pyrophosphate scanning (PYP) plotted against the average value measured by these techniques.

values. The size of the infarct measured by peak creatine kinase correlated only moderately with the volume of the infarct measured by pyrophosphate ($r = 0{\cdot}53$, $0{\cdot}02 > p > 0{\cdot}01$) and by magnetic resonance imaging ($r = 0{\cdot}52$, $0{\cdot}05 > p > 0{\cdot}02$). The correlations were weakened by the presence of two particularly high creatine kinase results (6955 and 6255) that were considerably greater than the other values. However, the total creatine kinase release, which included these two values, correlated well with the infarct size measured by both pyrophosphate ($r = 0{\cdot}75$, $0{\cdot}01 > p > 0{\cdot}001$) and magnetic resonance imaging ($r = 0{\cdot}62$, $0{\cdot}05 > p > 0{\cdot}02$). The residual left ventricular function measured by radionuclide ventriculography correlated significantly with the volume of infarct measured by both magnetic resonance ($r = 0{\cdot}79$, $p < 0{\cdot}001$) and pyrophosphate imaging ($r = -0\ 79$, $p < 0{\cdot}001$). There was also a good correlation between the left ventricular ejection fraction and the peak creatine kinase release ($r = -0{\cdot}63$, $0{\cdot}01 > p > 0{\cdot}001$), but a better correlation was obtained with the total creatine kinase release ($r = -0{\cdot}78$, $0{\cdot}01 > p > 0{\cdot}001$).

Discussion

The primary determinant of prognosis after acute myocardial infarction is the size of the area of infarction.[13–15] However, despite its importance, routine clinical measurement of infarct size has not been achieved. The techniques currently used are indirect and may be misleading after thrombolytic therapy. Peak serum creatine kinase values are more important. Analysis of creatine kinase MB release curves correlates well with histological infarct size and provides prognostic information.[16–18] However, after thrombolytic therapy there is an early accelerated "washout" of cardiac enzymes, presumably when blood flow is restored through partially necrotic myocardium.[19] Electrocardiographic techniques are used to map the extent of infarction but are inaccurate in assessing small non-transmural or posterior lesions.[20 21] Echocardiography is mainly of use in determining areas of wall thinning, dyskinesis, or akinesis, and hence also has major limitations. Residual ventricular function gives an indication of myocardial damage but is unreliable when there has been previous infarction. Tissue characterisation by any imaging technique remains an elusive goal.

Since the introduction of single photon emission tomography, pyrophosphate imaging has been considered a sensitive method for the diagnosis and measurement of acute myocardial infarcts.[22] The use of single photon emission tomography has allowed more accurate detection of posterior, inferior, and small subendocardial infarcts, particularly after the addition of blood pool overlay.[23] These data correlated well with the histological findings in animals,[23] and with analysis of serum creatine kinase MB release and residual left ventricular function in humans.

There are certain limitations to pyrophosphate imaging. The delivery of the radionuclide to the centre of a large infarct may be incomplete.[24] Our single photon emission tomographic technique overcomes this by measuring the volume defined by pyrophosphate rather than by quantifying the amount of isotope concentrated in the unevenly perfused tissue. More uniform labelling can be achieved by antimyosin antibodies, labelled with indium, but the poorer imaging characteristics of indium offset this advantage. Radionuclide imaging also involves exposure to a significant radiation dose and is only useful for up to five days after infarction, whereas our own work, performed in human subjects, showed that the maximum increase in T1 is not obtained for up to five days after infarction and persists for a long time thereafter.[25]

To determine the extent of myocardial

Correlations between measurements of infarct size, left ventricular ejection fraction (%), and release of creatine kinase MB (U/l)

	MRI infarct size	*^{99m}Tc PYP infarct size*	*LV ejection fraction*	*Peak creatine kinase*
LV ejection fraction	n = 18 r = −0 79 p < 0 001	n = 18 r = −0 79 p < 0 001		
Peak creatine kinase	n = 18 r = 0 52 0 05 > p > 0 02	n = 18 r = 0 53 0 02 > p > 0 001	n = 17 r = −0 63 0 01 > p > 0 001	
Total creatine kinase	n = 11 r = 0 62 0 05 > p > 0 02	n = 11 r = 0 75 0 01 > p > 0 001	n = 11 r = −0 78 0 01 > p > 0 001	n = 11 r = 0 93 p < 0 0001

LV, left ventricle, MRI, magnetic resonance imaging; PYP, pyrophosphate infarction by magnetic resonance imaging, we had to define T1 values for normal myocardium. Because the measured T1 values obtained from our system varied with repetition time it was essential to define a threshold limit for each individual patient. Although normal myocardium was identified subjectively the inter observer variability of 10·1% suggests that this is an acceptable method. In this study we related the volume of infarcted myocardium measured by magnetic resonance imaging five to seven days after infarction to several variables that also reflect infarct size.

We chose to obtain the magnetic resonance images at this stage because our previous work had shown this to be the time of maximal change. We studied patients with their first myocardial infarction so that preservation of ventricular function after infarction would negatively correlate with infarct size. In addition, because our patients were not treated with thrombolytic therapy the creatine kinase kinetics would be unaltered. Our results indicate that with a low field magnetic resonance imaging system T1 maps provide estimates of infarct size that agree closely with other techniques. We found a good agreement between magnetic resonance and pyrophosphate imaging and both these techniques correlated well with depressed ventricular function measured after infarction. Poorer correlations were obtained with peak creatine kinase but these were improved in the group of patients for whom enough data points were available to calculate the total release of creatine kinase MB.

We expect that the use of a 128 × 128 pixel matrix and a reduced slice thickness will improve the precision of infarct size measurement by magnetic resonance imaging although it will increase the examination time. Many factors, such as the field strength and the imaging pulse sequence, can alter the ability to detect myocardial damage. Currently the second or third echo of a multiple spin echo sequence is widely used to detect myocardial infarction, but particularly at high field strengths a paramagnetic contrast agent, such as gadolinium diethylenetriamine pentaacetic acid may then be required to demonstrate areas of damage.[26] This study shows the ability of a low field system with a saturation recovery-inversion recovery plus sequence to measure human infarct size and avoid the routine use of paramagnetic contrast agents. Because T1 values remain raised for the first three months after infarction,[25] this technique will provide information on infarct size in the convalescent period.

We thank Mrs R H B Armstrong and Miss F Taddei for their excellent technical help This work was supported in part by the British Heart Foundation

1 Gruppo Italiano per lo Studio della Streptochinasi nell' Infarto Miocardico (GISSI). Effectiveness of intravenous thrombolytic treatment in acute myocardial infarction. *Lancet* 1986;i:397–401.

2 ISIS-2 (Second International Study of Infarct Survival) Collaborative Group. Randomised trial of intravenous streptokinase, oral aspirin, both, or neither among 17,187 cases of suspected acute myocardial infarction· ISIS-2 *Lancet* 1988;ii 349–60

3 White HD, Norris RM, Brown MA, Takayama M, Maslowski A, Bass NM, *et al* Effects of intravenous streptokinase on left ventricular function and early survival after myocardial infarction *N Engl J Med* 1987, 317 855–8

4 Rokey R, Verani MS, Bolli R, Kuo LC, Ford JJ, Wendt RE, *et al* Myocardial infarct size quantification by MR imaging early after coronary artery occlusion in dogs *Radiology* 1986,158 771–4.

5 Caputo GR, Sechtem V, Tscholakoff D, Higgins CB Measurement of myocardial infarct size at early and late time intervals using NMR imaging An experimental study in dogs. *Radiology* 1987,149.237–43

6 Been M, Smith MA, Ridgway JP, Brydon JWE, Douglas RHB, Kean DM, *et al*. Characterisation of acute myocardial infarction by gated magnetic resonance imaging *Lancet* 1985,ii:348–50.

7 Tscholakoff D, Higgins CB, Sechtem U, Caputo G, Derugin N MRI of reperfused myocardial infarct in dogs. *AJR* 1986;146:925–30

8 Smith MA, Ridgway JP, Brydon JWE, Been M, Douglas RHB, Kean DM, *et al*. ECG gated T1 images of the heart *Phys Med Biol* 1986;59 603–7

9 Hutchinson JMS, Smith FW In. Partain CL, James AE, Rollo FD, Price RR *Nuclear magnetic resonance (NMR) imaging* Philadelphia: Saunders, 231–49.

10 Jansen DE, Corbett JR, Wolfe CL, Lewis SE, Gabliani G, Filipchuk N, *et al* Quantification of myocardial infarction a comparison of single photon-emission computed tomography with pyrophosphate to serial plasma MB-creatine kinase measurements *Nucl Cardiol* 1985,72 327–33.

11 Muir AL, Hannan WJ, Sapru RP, Boardman AK, Wraith PK, Brash HM The effects of isoprenaline, atropine and dobutamine on ventricular volume curves by radionuclide ventriculography. *Clin Sci* 1980,58·357–64

12 Bland JM, Altmann DG. Statistical methods for assessing agreement between two methods of clinical measurement *Lancet* 1986;i 307–10

13 Dewhurst NG, Muir AL. Comparative prognostic value of radionuclide ventriculography at rest and during exercise in 100 patients after first myocardial infarction *Br Heart J* 1983;49 111–21.

14 Page DL, Caulfield JB, Kaster JA, DeSanctis RW, Sanders CA Myocardial changes associated with cardiogenic shock *N Engl J Med* 1971,285.133–7.

15 Alonso DR, Scheidt W, Post M, Killip T. Pathophysiology of cardiogenic shock. Quantification of myocardial necrosis: clinical, pathological, and electrocardiographic correlations. *Circulation* 1973,48:588–96

16 Shell WE, Kjekshus JK, Sobel BE Quantitative assessment of the extent of myocardial infarction in the conscious dog by means of analysis of serial changes in serum creatine phosphokinase activity *J Clin Invest* 1971,50 2614–24.

17 Bleifeld WH, Hanrath P, Mathey D Serial CPK determinators for evaluation of size and development of acute myocardial infarction. *Circulation* 1976,53(suppl 1) 108–11.

18 Kluge WF. Prognostic value of serum creatine phosphokinase levels in myocardial infarction *Northwest Med* 1969,68 847–53.

19 I.S.A.M. Study Group A prospective trial of intravenous streptokinase in acute myocardial infarction (I S A M.) mortality, morbidity, and infarct size at 21 days. *N Engl J Med* 1986,23 1465–71

20 Muller JE, Maroko PR, Braunwald E. Evaluation of precordial electrocardiographic mapping as a means of assessing changes in myocardial ischaemic injury. *Circulation* 1975, 52 16–27

21 Murray RG, Peshock RM, Parkey RW, Bonte FJ, Willerson JT, Blomquist CG. ST iso-potential precordial surface maps in patients with acute myocardial infarction *J Electrocardiol* 1979,12:55–64

22 Corbett JR, Lewis M, Willerson JT, Nicod PH, Huxley RL, Simon T, *et al*. Technetium-99m pyrophosphate imaging in acute myocardial infarction Comparison of planar images with single-photon tomography with blood pool overlay *Circulation* 1984,69 1120–8.

23 Lewis SE, Devous MD, Corbett JR, Izquierdo C, Nicod P, Wolfe CL, *et al* Measurement of infarct size in acute canine myocardial infarction by single-photon emission computed tomography with technetium-99m pyrophosphate. *Am J Cardiol* 1984,54.193–9

24 Buja LM, Parkey RW, Stokey EM, Bonte FJ, Willerson JT Pathophysiology of technetium-99m pyrophosphate and thallium-201 scintigraphy of acute myocardial infarcts in dogs. *J Clin Invest* 1976,57 1508–22

25 Been M, Smith MA, Ridgway JP, Douglas RHB, de Bono DP, Best JJK, *et al*. Serial changes in the T_1 magnetic relaxation parameter after myocardial infarction in man. *Br Heart J* 1988,59:1–8.

26 Brown JJ, Higgins CB Myocardial paramagnetic contrast agents for MR imaging. *AJR* 1988;151 865–72

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Myocardial bridges: morphological and functional aspects

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Abstract

***Objective*—To assess the arrangement of myocardial bridges.**

***Design*—A necropsy study of 90 consecutive hearts (56 male, 34 female).**

***Results*—Myocardial bridges, either single or multiple, were seen in 50 (55·6%) of the 90 hearts. The left anterior descending artery was the most commonly affected artery. Thirty five of the 50 hearts which contained in total 41 muscle bridges were dissected further with a magnifying glass. Two different types of muscle bridges could be identified. Thirty one of these 41 myocardial bridges were superficial, crossing the artery transversely towards the apex of the heart at an acute angle or perpendicularly. The remaining 10 myocardial bridges crossed the left anterior descending coronary artery and surrounded it by a muscle bundle that arose from the right ventricular apical trabeculae and crossed the artery transversely, obliquely, or helically before terminating in the interventricular septum.**

***Conclusions*—The superficial type of myocardial bridge does not seem to constrict the artery during systole but the deep muscle bridges, by virtue of their relation with the left anterior descending coronary artery, could twist the vessel and thus compromise its diastolic flow. This may result in ischaemia.**

Reyman in 1737 and Black in 1805 described an anatomical curiosity—the overlaying of the left anterior descending coronary artery by a muscular bridge.[1,2] Since then there have been further reports[3,4] and some investigators have described acute myocardial infarction in young patients in whom no coronary atherosclerosis was identifiable but in whom muscle bridges were found and the cause of the infarction was directly referrable to the myocardial bridge.[5,6] There have been no detailed studies, however.

We have examined and classified myocardial bridges, particularly in terms of their relation to the left anterior descending coronary artery and have examined the haemodynamic implications these findings may have for ischaemic heart disease.

Patients and methods

We studied 90 hearts (56 male, 34 female) removed consecutively at necropsy. The individual ages ranged from a stillbirth to 84 years and in none was there a history of preceding established cardiac disease and death was not referrable to cardiac causes. Myocardial bridges were identified in 50 hearts. Thirty five of these hearts were examined further by hand lens dissection. Thirteen of the remaining 15 hearts, in which the left anterior descending coronary artery was directly related to a muscle bundle, were assessed histologically. After fixation, five were embedded in paraffin and 10 μm sections were cut, and four were embedded in 8% celloidin and 100 μm sections were cut. The sections were then stained by azan and resorcin fuschin and the azan and Weigert method respectively to demonstrate connective and elastic tissue. Segments of four hearts which included muscle bridges were cut at 60 μm in a cryostat and stained by Sudan III to assess the adipose tissue interposed between the artery and the muscle bridge. The remaining two hearts were set aside for ultrastructural investigation.

STATISTICAL TESTS

We used Student's *t* test for paired and unpaired samples with Fisher tests for variance and multiple comparison analysis. P values $<0·05$ were considered significant.

Results

Thirty two of the 50 hearts that contained muscle bridges came from male subjects. In 35 hearts the bridges were single, affecting solely the left anterior descending coronary artery; 10 hearts contained two muscle bridges and five hearts contained three muscle bridges. These multiple muscle bridges affected either the same vessel or different coronary arteries or their branches. Significantly longer muscle bridges were seen in the 21–50 age group than in the hearts removed from subjects 0–20 years (table 1). There was no statistical difference between the length of myocardial bridges in male and female subjects (table 2). Shorter muscle bridges were more common (table 3 and fig 1).

Table 1 Average (SD) length of myocardial bridges at different ages

Age (yr)	*Average length (cm)*
0–20	1·36 (0·479)
21–50	2·99 (1·710)
51–90	2·07 (1·419)

Only the difference between the 0–20 and 21–50 age groups ($F = 5·29$) was statistically significant ($p = 0·0094$).

Table 2 Average (SD) length of the myocardial bridges in male and female hearts

	Average length (cm)
Male	2·16 (1·455)
Female	2·03 (1·438)

$t = 0{\cdot}28$; $p > 0{\cdot}05$.

At hand lens dissection 41 muscle bridges were detected and were classified as superficial if the left anterior descending coronary artery ran on the interventricular groove and was crossed by the muscle bundle perpendicularly or at an acute angle before deviating to the apex of the heart (fig 2). This type was the more common and was identified in 31 (75·6%) of the bridges. The remaining 10 muscle bridges (24·4%) were classified as deep: the left anterior descending coronary artery deviated towards the right ventricle and was deeply situated on the interventricular septum where it was crossed transversely, obliquely or helically by a longitudinal bundle arising from the apex of the right ventricle and inserting into the interventricular septum (figures 3A and B). Close scrutiny showed that some fibres surrounded the artery. This deep variant was seen less frequently and had longer muscle bundles than its superficial counterpart (table 3). Histological studies showed that there was no direct contact between the muscle bridge and the adventitial wall of the associated artery and that adipose, neural, and loose connective tissues were interposed between the muscle bridge and the related artery.

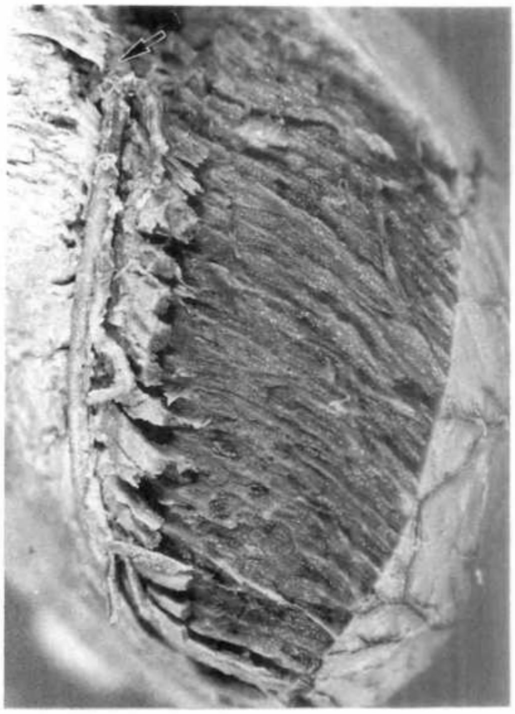

Figure 2 Dissected heart showing a 1·2 cm superficial myocardial bridge overlying the left anterior descending coronary artery (arrow) which runs throughout its course on the interventricular groove.

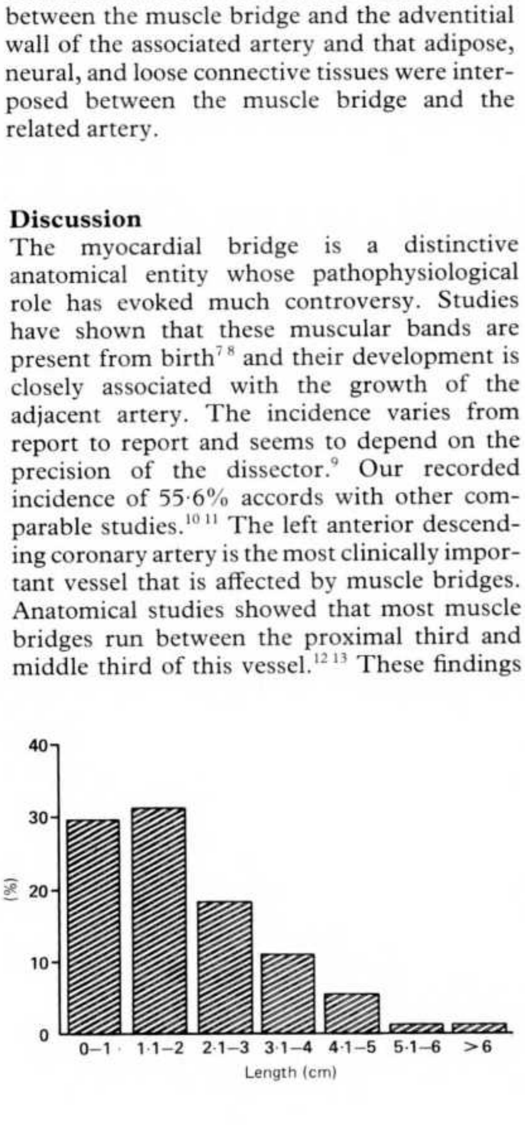

Figure 1 Graph showing incidence of muscle bridges and their length.

Discussion

The myocardial bridge is a distinctive anatomical entity whose pathophysiological role has evoked much controversy. Studies have shown that these muscular bands are present from birth[7,8] and their development is closely associated with the growth of the adjacent artery. The incidence varies from report to report and seems to depend on the precision of the dissector.[9] Our recorded incidence of 55·6% accords with other comparable studies.[10,11] The left anterior descending coronary artery is the most clinically important vessel that is affected by muscle bridges. Anatomical studies showed that most muscle bridges run between the proximal third and middle third of this vessel.[12,13] These findings accord with our own observations. The association of myocardial bridges with ischaemia is well established and symptoms have been relieved by surgical excision of the muscle bridge.[14,15] Hill *et al* showed that when the left anterior descending coronary artery runs underneath a muscle bridge it can be distorted in systole with a delay in diastolic relaxation. They also found that surgical resection of the muscle bridge often relieved the functional disturbance.[16] However, some individuals with muscle bundles are symptom free.[17] Various workers have attempted to classify the anatomical distribution of muscle bridges. Geiringer defined two types: in the first the left anterior descending coronary artery was sited deep in the interventricular groove with the muscle bridge surrounding it and in the second variant, which he considered to be more common, the muscle bridge arose from the trigonum fibrosum and invested the left anterior descending coronary artery as it passed to the apex of the heart.[3] We would classify these two types as superficial.

We consider the distinction between superficial and deep muscle bridges to be important in ischaemia and our classification may explain why some demonstrable muscle bridges do not cause symptoms. We showed that deep muscle bridges surround the left anterior descending coronary artery with helices of muscle fibres and we speculate that this may distort or compress the adjacent artery. Porstmann and Iwig recognised the usefulness of angiography in permitting in vivo visualisation of the myocardial bridge.[18] Amplatz and Anderson too studied myocardial bridges angiographically.[19] Angelini and his colleagues in their comprehensive review described how systolic

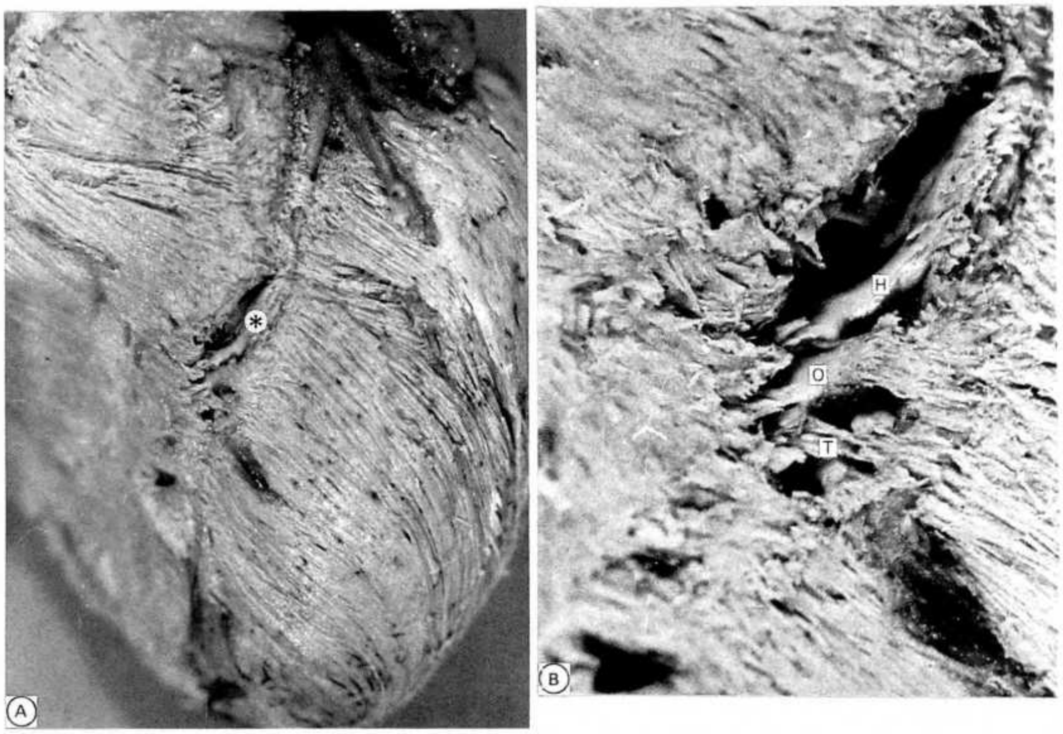

Figure 3 (A) Dissected heart showing a 6·2 cm deep myocardial bridge overlying the left anterior descending coronary artery. The path of the artery deviates from the interventricular groove towards the right ventricle where it is surrounded by a muscle bundle arising from the right ventricular apical trabeculae (*). (B) Close up view showing the oblique (O), helical (H) and transverse (T) orientation of the surrounding muscle bundle.

narrowing and kinking are useful angiographic evidence of myocardial bridges.[20]

Angelini *et al* commented on the disparity between the high incidence of myocardial bridges reported from anatomical studies and the lower angiographic incidence. Furthermore, they noted that angiographic evidence of myocardial bridges may depend on several factors, including the length of the bridge, the precise orientation of the bridge fibres in relation to the left anterior descending coronary artery, and the nature of the tissue interposed between the myocardial bridge and the adjacent artery. We believe that the disparity in the incidence reported from anatomical and angiographic studies depends on the length of the muscle bridge and that angiography detects only the deep myocardial bridges, which we noted were significantly larger and more likely to interfere with coronary flow. Ishimori *et al* reported that administration of glyceryl trinitrate to some patients unmasked angiographic narrowing of the left anterior descending coronary artery in systole,[21] while the use of vasoactive drugs in patients with muscle bundles, has resulted in an episode of cardiac ischaemia in some subjects.[22 23] We suggest that in patients with compression caused by the deep muscle bundle arrangement dilatation of the left anterior descending coronary artery may be unsuccessful.

We conclude that superficial or deep myocardial bridges form in utero at the time of cardiac development. In most individuals they do not cause symptoms but particularly in those with deep myocardial bridges, the anatomical relation of the myocardial fibres can distort the artery that can be identified angiographically. The possibility of myocardial bridges should be borne in mind in individuals with ischaemia but no evidence of coronary atherosclerosis.

Table 3 Average (SD) length of myocardial bridges according to path

	Average length (cm)
Superficial	1·53 (0·895)
Deep	3·95 (1·251)

t = 6·71; p < 0·0001.

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1 Reyman HC. Dissertatio de vasis cordis propriis. *Haller, Bibl Anat* 1737;**2**:366.
2 Black S. A case of angina pectoris with a dissection. *Memoirs of the Medical Society of London* 1805;**6**:41.
3 Geiringer E. The mural coronary. *Am Heart J* 1951;**41**: 359–68.
4 Edwards JC, Burnsides G, Swarm RL, Bansing AI. Arteriosclerosis in the intramural and extramural portions of coronary in the human heart. *Circulation* 1956;**13**: 235–41.
5 Vasan RS, Bahl VK, Rajani M. Myocardial infarction associated with a myocardial bridge. *Int J Cardiol* 1989;**25**:240–1.
6 Bestetti RB, Costa RS, Zucolotto S, Oliveira JSM. Fatal outcome associated with autopsy proven myocardial bridging of the left anterior descending coronary artery. *Eur Heart J* 1989;**10**:573–6.
7 von Polácek P. Relation of myocardial bridges and loops on the coronary arteries to coronary occlusions. *Am Heart J* 1961;**61**:44–52.
8 Visscher DW, Miles BL, Waller BF. Tunnelled ("bridged") left anterior descending coronary artery in a newborn without clinical or morphologic evidence of myocardial ischaemia. *Cathet Cardiovasc Diagn* 1983;**9**:493–6.
9 von Polácek P, Zechmeister A. The occurrence and significance of myocardial bridges and loops on coronary arteries. Opuscola Cardiologica. Acta Facultatis Medicae Universitatis Brunensis, Brno, 1968.
10 Hansen BF. Myocardial covering on epicardial coronary arteries. Prevalence, localization and significance. *Scand J Thorac Cardiovasc Surg* 1982;**16**:151–5.
11 Ishii T, Hosoda Y, Osaka T, *et al*. The significance of myocardial bridge upon atherosclerosis in the left anterior descending coronary artery. *J Pathol* 1986;**148**:279–91.
12 Bezerra AJC, Prates JC, Didio LJA. Incidence and clinical significance of bridges of myocardium over the coronary arteries and their branches. *Surg Radiol Anat* 1987;**9**: 273–80.
13 Reig J, Loncan MP, Martin S, Binia M, Petit M, Domenech JM. Ponts myocardiques. Incidence et relation avec certaines variables coronariennes. *Arch Anat Histol Embryol* 1986;**69**:101–10.
14 Marshall ME, Headley RN. Intramural coronary artery as a cause of unstable angina pectoris. *South Med J* 1978; **71**:1304–6.
15 Teixeira JR, Aldrovando J, Santos PSF, *et al*. Artéria coronária descendente anterior com trajeto intramiocár-

dico: estudo anatômico e implicações cirúrgicas. *Arq Bras Cardiol* 1979;**33**(suppl 1):334–9.

16 Hill RC, Chitwood WR Jr, Bashore TM, Sink JD, Cox JL, Wechsler AS. Coronary flow and regional function before and after supraarterial myotomy for myocardial bridging. *Ann Thorac Surg* 1981;**31**:176–81.

17 Loures JBL, Souza JEMR, Pimentel WAF, *et al.* Estudo hemodinâmico e metabólico de pacientes com ponte miocárdica na artéria descendente anterior. *Arq Bras Cardiol* 1978;**31**:159–65.

18 Porstmann W, Iwig J. Die intramurale Koronarie im Angiogramm. *Fortschr Röntgenstr* 1960;**92**:129–32.

19 Amplatz K, Anderson R. Angiographic appearance of myocardial bridging of the coronary artery. *Invest Radiol* 1968;**3**:213–5.

20 Angelini P, Trivellato M, Donis J, Leachman RD. Myocardial bridges: a review. *Prog Cardiovasc Dis* 1983;**26**:75–88.

21 Ishimori T, Raizner AE, Chahine RA, Awdeh M, Luchi RJ. Myocardial bridges in man: clinical correlations and angiographic accentuation with nitroglycerine. *Cathet Cardiovasc Diagn* 1977;**3**:59–65.

22 Pichard AD, Casanegra P, Marchant E, Rodriguez JA. Abnormal regional myocardial flow in myocardial bridging of the left anterior descending coronary artery. *Am J Cardiol* 1981;**47**:978–82.

23 Carvalho VB, Macruz R, Décourt LV, *et al.* Hemodynamic determinants of coronary constriction in human myocardial bridges. *Am Heart J* 1984;**108**:73–80.

PLANTS IN CARDIOLOGY

Royal Botanic Gardens, Kew.

Atropa belladonna L.
Stephenson J, Churchill JM. *Medical botany*. London: 1834, volume 1, plate 1.

Atropine

Atropine is obtained from the leaf and berries of *Atropa belladonna* (Solanaceae), the deadly nightshade, an herbaceous plant of central and southern Europe. It is very poisonous and Linnaeus named it after one of the Fates, Atropus, who cut the thread of life. Though it was popular for deliberate poisoning it was avoided medicinally except for external use. The leaf was used to dilate the pupil for cataract extraction, and as a liniment for rheumatism. A large pupil was once held to enhance female beauty, hence belladonna. Nightshade is a curious word which may allude to the narcotic property of the black berries.

Atropine was isolated in 1831, and in 1867 von Bezold showed that it blocked the cardiac effects of vagal stimulation. Sir James Mackenzie (1853–1925) used it widely in his arrhythmia work. He showed that it would revert partial though not complete heart block. He also studied its effect on the rate in digitalised patients with atrial fibrillation and submitted a paper on this subject to *Heart*. The editor, Thomas Lewis, rejected it and this infuriated Mackenzie who replied "You might as well put upon the forefront of the journal 'No articles will be accepted which are not in accordance with the (temporary) beliefs of the Editor' " (McMichael J, *Journal of the Royal College of General Practitioners* 1981;**31**:402–6). Atropine was employed with minimal success to prevent Stokes-Adams attacks and it was little used in cardiology until the introduction of cardiopulmonary resuscitation.

The family Solanaceae is distributed worldwide and has over 2000 species, which include tomato, potato, and tobacco. The invaluable drug hyoscine (scopolamine) is found in *Mandragora officinarum* (mandrake) and in *Datura stramonium* (thornapple). Nowadays atropine and hyoscine are obtained commercially from an Australian tree of this family *Duboisia myoporoides* (corkwood) whose narcotic property was discovered by the aboriginals.

A HOLLMAN

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Pregnancy outcome and Ebstein's anomaly

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Abstract

***Background*—Ebstein's anomaly is an uncommon congenital cardiac abnormality that may be associated with cyanosis and arrhythmias. For those female patients with the anomaly who survive to adult life there is little information available about pregnancy, maternal complications, and fetal outcome. This study was designed to address this issue so that these patients can receive appropriate advice and management.**

***Methods and results*—Forty two pregnancies in 12 women with Ebstein's anomaly were studied. The mothers' cardiac lesions were assessed on the basis of symptoms, the presence of cyanosis or arrhythmia, and by echocardiographic grading of severity. In the absence of important maternal cyanosis or arrhythmia, pregnancy was well tolerated. Neonatal outcome was good though there was an increased risk of prematurity and dysmaturity in the babies born to mothers with cyanosis.**

***Conclusions*—This study indicates that women with Ebstein's anomaly who reach child-bearing age can be advised that pregnancy is likely to be well tolerated with good fetal outcome. Maternal arrhythmia or cyanosis are indications for closer maternal and fetal observation.**

In 1866, Wilhelm Ebstein, only five years after his graduation from medical school, first described the clinical and anatomical features of this congenital anomaly of the tricuspid valve. The patient he studied was a 19 year old labourer who died after suffering increasing symptoms of palpitation, dyspnoea, and cyanosis.[1]

Pregnancy in women with Ebstein's anomaly has been mentioned briefly in a few reports.[2-4] The numbers are small, however, and there is little information on pregnancy and fetal outcome in this disorder. A considerable proportion of women with the anomaly reach childbearing age and it is important that they receive appropriate advice in the reproductive years.

Patients and methods

Information was obtained by review of medical, obstetric, and neonatal records, and where possible patients were interviewed personally. The 12 women we studied had been referred for assessment to the Prince Charles Hospital, which is the cardiothoracic centre for the state of Queensland. They include all cases that could be found in the hospital records of women with Ebstein's anomaly who survived infancy. One case was excluded because of other major congenital anomalies (coarctation with corrected transposition of the great arteries).

Electrocardiograms, echocardiograms, and radiological data were reviewed. The anatomical severity of the lesion was determined by echocardiographic assessment and measurement of the ratio of atrialised right ventricle to the total right ventricle (aRV/RV) by Shina's method.[5]

Results

PATIENTS

In six women the diagnosis was not known at the time of pregnancy. In one patient the diagnosis was made during her second pregnancy. Two women had associated cyanosis and two had Wolff-Parkinson-White syndrome. The severity of tricuspid valve displacement ranged from a ratio of atrialised right ventricle to right ventricle of 16% to 71%. Only one patient had an associated congenital heart lesion which was pulmonary stenosis.

PREGNANCY OUTCOME

There were 42 pregnancies. Most of these were well tolerated with 36 live births (table 1). There were five miscarriages (four in patient 12), one ectopic pregnancy, and one neonatal death. Four pregnancies were complicated by premature labour and one by antepartum haemorrhage.

Most infants were born by spontaneous vaginal delivery. Three pregnancies in women known to have Ebstein's anomaly were induced because of maternal dyspnoea. There were four forceps deliveries and three caesarean sections. Epidural anaesthesia was used in only two deliveries, one by forceps and the other by caesarean section. General anaesthetics were given for the other two caesariean sections. No complications occurred with either form of anaesthesia.

Antibiotic cover was given in 12 deliveries where the diagnosis of Ebstein's anomaly in the mother was known, and in two because of the presence of a cardiac murmur. There were no cases of endocarditis.

Most women reported symptoms of dyspnoea in the third trimester of pregnancy. Only patients 3 and 4 were treated with digoxin and none required diuretics. Several women experienced palpitation but there were no

Table 1 Obstetric and infant outcome in women with Ebstein's anomaly

		Patients				*Obstetric outcome*					*Infant outcome*		
Patient	*Age*	*Age at diagnosis (yr)*	*aRV:RV (%)**	*Cyanosis*	*WPW*	*No of pregnancies*	*Live births*	*SVD*	*Forceps*	*Caesarean section*	*Premature*	*SFGA*	*Comments*
1	31	7	16		+	2	2	—	1	1	1	—	
2	38	10	53			2	2	1	1	—	—	1	
3	18	16	71	+		1	1	—	—	1	1	—	
4	26	21	50			4	4	2	2	—	2	—	
5	38	24	66		+	4	4	4	—	—	—	—	
6	51	27	29			6	4	4	—	—	—	1	1 miscarriage 1 ectopic pregnancy
7	Dead	48	44			2	2	2	—	—	?	?	
8	57	50	43			4	4	4	—	—	—	1	Pulmonary valvotomy after first pregnancy
9	54	53	47			4	4	4	—	—	—	—	
10	69	56	66	+		2	2	2	—	—	1	1	
11	69	68	42			1	1	—	—	1	—	—	
12	Dead	73	65			10	6	6	—	—	?	?	4 miscarriages, 1 neonatal death

* Ratio of atrialised right ventricle to right ventricle (aRV/RV) expressed as a percentage (%).
SVD, spontaneous vaginal delivery; SFGA, small for gestational age (no infants were both premature and small for gestational age).
? Information on prematurity and dysmaturity not available.

documented arrhythmias and only patient 1 required treatment.

Two women had considerable problems during pregnancy related to their cardiac anomaly. Case 1 who had Wolff-Parkinson-White syndrome but relatively mild valve displacement was unwell with arrhythmias during both her pregnancies. This was in spite of prior His ablation surgery and antiarrhythmic treatment. She required a forceps delivery in the first pregnancy because of symptomatic paroxysmal atrial tachycardia in the second stage of labour. In her second pregnancy she required two admissions for control of arrhythmia and cardioversion for resistant atrial fibrillation at 34 weeks followed by urgent caesarean section.

In contrast, the dominant features in case 3 were cyanosis and severe displacement of the tricuspid valve, with a ratio of atrialised right ventricle to right ventricle of 71%. This patient required admission at 26 weeks' gestation with grade III New York Heart Association symptoms of dyspnoea and progressive cyanosis, and she underwent a caesarean section at 36 weeks' gestation with resolution of her symptoms.

INFANT OUTCOME

Five of the 36 live born infants were premature (less than 37 weeks' gestation), with birth weights ranging from 1360 g to 2500 g (table 2). Two of the three infants born to mothers with cyanosis were in this group. A further four term infants were small for gestational age (less than the tenth percentile) including the third infant born to a mother with cyanosis (table 3).

Only one neonatal death occurred (cause unknown) in a twin born at term. All other infants survived and are alive and well and none has congenital cardiac or other anomalies.

Discussion

In pregnancy several important physiological changes occur within the cardiovascular system. Plasma volume increases by 40%, reaching a maximum at 30 weeks. A smaller rise in red cell mass of 20 to 30% results in the dilutional anaemia of pregnancy. Cardiac output rises by 40%, with an increase in both stroke volume and heart rate[6] and with an accompanying rise in circulating catecholamine concentrations.[7] However, despite the increase in cardiac output, systemic blood pressure is lower than in the non-pregnant state, indicating a considerable reduction in peripheral vascular resistance due to peripheral vasodilation and placental shunting.[7]

In patients with Ebstein's anomaly, these physiological changes may have appreciable adverse haemodynamic consequences. In the presence of impaired right ventricular size and function, the increased stroke volume may be poorly tolerated and result in worsening tricuspid incompetence, raised right atrial pressures, and increased right to left shunting. Complications of pregnancy and delivery such as haemorrhage may not be well tolerated by these

Table 2 Features and reason for delivery of infants who were born prematurely (less than 37 weeks' gestation)

Gestation (w)	*Birth weight (g)*	*Features and reason for delivery*
28	1360	Spontaneous preterm labour
32	1475	Spontaneous preterm labour, maternal cyanosis
34	2540	Urgent caesarean section, resistant maternal arrhythmias
36	2480	Spontaneous preterm labour
36	2170	Caesarean section for worsening maternal dyspnoea and cyanosis

Table 3 Features and reason for delivery of infants born small for gestational age (birth weight less than the 10th percentile for gestation

Gestation (w)	*Birth weight (g)*	*Features and reason for delivery*
39	1815	Spontaneous vaginal delivery, maternal pulmonary stenosis corrected after 1st pregnancy
39	2310	Maternal dyspnoea, spontaneous vaginal delivery
40	2615	No maternal symptoms, forceps delivery for failure to progress
40	2950	Maternal cyanosis, spontaneous vaginal delivery

mothers where right ventricular dysfunction may impair the patient's capacity to cope with the large volume shifts associated with fluid resuscitation.

In the present series, pregnancy was generally well tolerated. Mild dyspnoea was a common symptom in the third trimester but no more troublesome than has been described in normal pregnancy.[8] Only in case 3 did overt symptoms of right heart failure develop. This mother had cyanosis and very severe displacement of the tricuspid valve. However, four patients who also had considerable displacement of the tricuspid valve tolerated pregnancy well. Therefore no correlation was demonstrated between symptoms and the degree of displacement of the tricuspid valve leaflet as described by Shina *et al.*[5]

Patients with Ebstein's anomaly are liable both to supraventricular and ventricular arrhythmias, and Wolff-Parkinson-White syndrome occurs in up to 20% of patients.[9] The raised concentrations of circulating catecholamines in pregnancy will exacerbate any predisposition to arrhythmias and major arrythmias may occur, particularly if there is maternal hypoxaemia or stress. One of our patients had severe arrhythmias in two pregnancies and required cardioversion despite antiarrhythmic treatment (digoxin, verapamil, flecainide). She had Wolff-Parkinson-White syndrome and in the non-pregnant state had sufficiently severe arrhythmias to warrant His ablation surgery.

Arrhythmias in patients with Ebstein's anomaly, however, are not an absolute contraindication to pregnancy. Various antiarrhythmic drugs have been used without adverse effects on the fetus—for example, propanolol, disopyramide, procainamide, flecainide, sotalol, and amiodarone.[10-12] Patient 5, who had no severe arrhythmias before pregnancy, shows that Ebstein's anomaly with Wolff-Parkinson-White syndrome may in fact be well tolerated. Therefore, advice regarding the risks of pregnancy depends in part on the capacity to achieve arrhythmia control in the non-pregnant state.

Maternal cyanotic congenital heart disease has been shown to be associated with prematurity and low birth weight and with infant survival rates of 50–55%.[2 3] The combined effects of maternal hypoxaemia and haemodynamic instability make the infant liable to intrauterine fetal growth retardation and even death. The three infants born to cyanosed mothers in our study were premature or dysmature, but all survived and did well.

No baby had congenital heart disease in this series. While the numbers are small, the rate of congenital heart disease seems to be low compared with published data rates of 2–14%.[3 13]

Obstetric complications were infrequent in the present series. Only one woman had mild pre-eclamptic toxaemia without a significant change in her symptoms. The miscarriage rate of 12% is similar to standard rates of 10% to 15%.[14] Despite the increased cardiovascular stress and major fluid shifts associated with labour and delivery, these final stages of pregnancy were well tolerated. Special intervention and monitoring were rarely used. The 7% caesarean rate and 9% forceps delivery rate compare favourably with standard rates of 5–20% and 5–15% respectively. Though antibiotic prophylaxis was given in only 14 of the 42 pregnancies there were no episodes of endocarditis, which accords with the reported low incidence.[3]

There are few published reports on pregnancy in women with Ebstein's anomaly. The largest series was reported by Radford *et al*, where successful pregnancy occurred in six women who had a total of 12 children.[4] In two large studies on congenital heart disease in pregnancy (total 357 women) five women had Ebstein's anomaly and three of them had cyanosis.[2 3] They had eight pregnancies and there were two fetal deaths, both in infants born to women with cyanosis. Several case reports emphasise the potential complications in pregnancy in women with Ebstein's anomaly.[15-17] However, in each one the patients were symptom free until the third trimester and mother and infant survived.

Though pregnancy was well tolerated in patients in this study and fetal outcome was good, five women including three in whom there were no strong medical or obstetric indications had been advised not to have further pregnancies because of their cardiac anomaly. This uncertainty about the natural history of the condition in pregnancy is reflected in a report of unnecessary termination of pregnancy because of the diagnosis of Ebstein's anomaly in the mother.[18]

The results of this study indicate that women with Ebstein's anomaly who reach childbearing age can be advised that pregnancy is likely to be well tolerated and fetal outcome good. The presence of arrhythmia or cyanosis in the mother is associated with increased maternal and fetal risk and are indications for closer maternal and fetal observation during pregnancy and delivery.

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1 Mann RJ, Lie JT. The life story of Wilhelm Ebstein (1836–1912) and his almost overlooked description of a congenital heart disease. *Mayo Clin Proc* 1979;**54**:197–203.
2 Copeland WE, Wooley CF, Ryan JM, Runco V, Levin HS. Pregnancy and congenital heart disease. *Am J Obstet Gynecol* 1963;**86**:107–10.
3 Whittemore R, Hobbins JC, Allen Engle M. Pregnancy and its outcome in women with and without surgical treatment of congenital heart disease. *Am J Cardiol* 1982;**50**:641–51.
4 Radford DJ, Graff RF, Neilson GH. Diagnosis and natural history of Ebstein's anomaly. *Br Heart J* 1985;**54**:517–22.
5 Shina A, Seward JB, Edwards WD, Hagler DJ, Tajik AJ. Two-dimensional echocardiographic spectrum of Ebstein's anomaly: detailed anatomic assessment. *J Am Col Cardiol* 1984;**3**:356–70.
6 McAnulty JH, Metcalfe J, Ueland K. Cardiovascular disease. In: Burrow GN, Ferris TF, eds. *Medical complications during pregnancy.* 2nd ed. Philadelphia: WB Saunders, 1982:145–68.
7 Gianopoulos JG. Cardiac disease in pregnancy. *Med Clin North Am* 1989;**73**:639–51.
8 Huff RW. Asthma in pregnancy. *Med Clin North Am*

1989,73:653–60.

9 Van Mierop LHS, Kutsche LM, Victorica BE. Ebstein's anomaly. In Adams FH, Emmanoulides GC, Riemenschneider TA, eds. *Moss' heart disease in infants, children and adolescents*. 4th ed. Baltimore. Williams and Wilkins, 1989 361–71.

10 Mitani GM, Steinberg I, Lien EJ, Harrison C, Elkayam U The pharmacokinetics of antiarrhythmic agents in pregnancy and lactation. *Clin Pharmocokinet* 1987;12:253–91.

11 Wagner X, Jouglard J, Moulin M, Miller AM, Petitjean J, Pisapia A. Co-administration of flecainide acetate and sotalol during pregnancy: lack of teratogenic effects, passage across the placenta, and excretion in human breast milk *Am Heart J* 1990,119:700–2.

12 Foster CJ, Love HG Amiodarone in pregnancy. Case report and review of the literature. *Int J Cardiol* 1988;20:307–16.

13 Nora JJ, Nora AH The evolution of specific genetic and environmental counselling in congenital heart disease. *Circulation* 1978;57:205–13.

14 Beischer NA, Mackay EV. *Obstetrics and the newborn* 2nd ed Sydney: Saunders, 1986:406, 422.

15 Waickman, LA, Skorton DJ, Varner MW, Ehmke DA, Goplerud CP. Ebstein's anomaly and pregnancy. *Am J Cardiol* 1984,53 357–8.

16 Linter SPK, Clarke K. Caesarean section under extradural analgesia in a patient with Ebstein's anomaly *Br J Anaesth* 1984·56:203–5

17 Halpern S, Gidwaney A, Gates B Anaesthesia for caesarean section in a preeclamptic patient with Ebstein's anomaly. *Can Anaesth Soc J* 1985;32·244–7.

18 Littler WA. Successful pregnancy in a patient with Ebstein's anomaly. *Br Heart J* 1970,32:711–3.

Br Heart J 1991;66:372–4

Doppler echocardiographic evaluation of pulmonary blood flow after the Fontan operation: the role of the lungs

D J Penny, A N Redington

Abstract

***Objective*—To document whether the act of respiration influences pulmonary blood flow in patients after the Fontan operation.**

***Design*—Prospective study in which patients acted as their own controls.**

***Setting*—Supraregional paediatric cardiology centre.**

***Patients*—Sixteen patients who had undergone atriopulmonary anastomosis (Fontan operation) for the treatment of congenital heart disease.**

***Intervention*—Doppler assessment of pulmonary artery flow patterns with a simultaneous respirometer, electrocardiogram and phonocardiogram.**

***Results*—Total (mean (1SD)) forward pulmonary flow was 63·6 (35)% higher during inspiratory cardiac cycles than during expiratory ones.**

***Conclusions*—The act of breathing provides an additional energy supply to pulmonary blood flow in patients after the Fontan operation.**

Since Fontan and Baudet's description of the atriopulmonary anastomosis for the palliation of complex congenital heart disease,[1] there has been considerable debate regarding the determinants of blood flow through a pulmonary vascular bed when no ventricular pumping chamber is present. For the most part this debate has centred around the importance of atrial contraction in providing an energy source for pulmonary blood flow. The potential contribution of the atrial pump to an atriopulmonary circulation was first suggested 36 years ago[2] and most recently re-emphasised in this journal.[3] Conversely, others have suggested that atrial activity provides no additional energy to pulmonary blood flow,[4 5] so that the Fontan circulation has been described as one for which the sole net energy supply originates in the left ventricle.[6]

While the role of the right atrium in providing energy to the Fontan circulation continues to be explored, the potential role of other possible energy sources must not be forgotten. We showed that respiratory effort seems to be a powerful determinant of pulmonary blood flow in patients after total cavopulmonary connection,[7] in which the right heart is completely bypassed. Furthermore, we attempted to augment the effect of normal respiration on the pulmonary circulation in these patients with negative extrathoracic pressure ventilation and we found that pulmonary blood flow increased with this technique.[8] Though the potential implications of respiratory effort for pulmonary blood flow in patients after the Fontan operation have been mentioned,[9] they have not been formally assessed.

We investigated whether respiratory effort influenced pulmonary blood flow in patients after the Fontan operation, in whom a subpulmonary atrium is incorporated into the pulmonary circulation.

Patients and methods

PATIENTS

Sixteen patients (11 male and five female; mean (1SD) age 119 (45·6) months) were studied 38·5 (31·5) months after atriopulmonary anastomosis. Nine patients had a preoperative diagnosis of tricuspid atresia, five had double inlet left ventricle, one had double inlet right ventricle, and one patient had double outlet right ventricle with abnormal insertion of the tricuspid valve tensor apparatus which precluded a biventricular repair. Atriopulmonary anastomosis was performed in all patients (by direct suture in eight and via an interposition homograft conduit in eight). The atrial septal defect was closed in all patients and the right atrioventricular valve orifice was closed in patients who had two atrioventricular valves.

MEASUREMENTS

Patients were studied at rest in a supine position during quiet respiration. Doppler echocardiograms were recorded from a parasternal or suprasternal position with a 5 MHz or 3·5 MHz transducer interfaced with a Toshiba SSH-160A ultrasound system. A pulsed wave, range gated Doppler sample volume was positioned in the pulmonary artery distal to the site of the atriopulmonary anastomosis. Simultaneous electrocardiograms, phonocardiograms, and a respirometer trace were recorded. Recordings were made at a paper speed of 100 mm/s.

ANALYSIS

Measurements were obtained over six cardiac cycles (three during inspiration and three during expiration). To separate the atrial contribution to pulmonary flow from that during the remainder of the cardiac cycle we drew a

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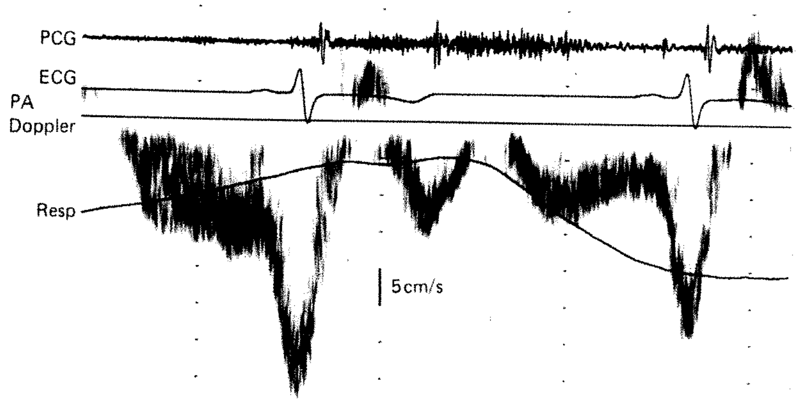

Figure Simultaneous pulmonary artery Doppler flow (PA Doppler), electrocardiogram (ECG), phonocardiogram (PCG), and respirometer (Resp) trace in a patient after the Fontan operation. During inspiration (upward deflection on the respirometer) the total forward pulmonary flow-velocity integral and peak forward flow velocity were increased.

vertical line to zero at the beginning of the onset of the waveform related to atrial systole.[3] We calculated the atrial contribution to pulmonary flow (%) as 100 × the velocity-time integral during atrial contraction, divided by the velocity-time integral of total forward pulmonary flow.[3] Peak forward flow velocity in the pulmonary artery was measured directly from the paper recordings.

Traces were digitised with a Summagraphics digitising plate, interfaced with a Prime 750 mainframe, so that the total pulmonary flow-velocity integral and its atrial component could be compared during inspiration and expiration. No attempt was made to calculate the area of the atriopulmonary anastomosis, which was assumed to remain constant throughout the cardiac and respiratory cycle. All indices were expressed as mean (1SD) and the statistical significance of differences between group means was assessed by Student's t test. Probability values $<0{\cdot}05$ were regarded as significant.

Results

PULMONARY DOPPLER FLOW

All patients were in sinus rhythm and a biphasic pattern of forward flow was seen in the pulmonary artery (fig). Low velocity forward flow occurred during ventricular systole and early diastole. During late diastole forward flow was augmented at the same time as atrial contraction, so that the atrial contribution to forward flow in the pulmonary artery during expiration was 51·4 (8·8)% of total forward flow.

EFFECT OF RESPIRATION

Total forward flow during inspiratory cardiac cycles was 63·6 (35)% higher than during expiratory ones ($p < 0{\cdot}001$). We saw a proportional increase in forward flow during atrial contraction, so that the contribution of atrial contraction to total flow was similar during inspiration (52·0 (10)%) and expiration (51·4 (8·8)%) ($p = 0{\cdot}693$) (fig).

Inspiration, furthermore, resulted in an increase in peak forward flow velocity during atrial systole from 39·8 (16·6) cm/s to 51·3 (19·9) cm/s ($p < 0{\cdot}001$).

EFFECT OF ATRIOVENTRICULAR CONNECTION

During expiration the atrial contribution to forward flow in the pulmonary artery tended to be higher in patients with double inlet ventricle (57·4 (6·7)%) than in patients with tricuspid atresia (48·6 (8·9)%), although thi difference did not reach statistical significance ($p = 0{\cdot}059$). Similarly, during inspiration, no significant difference in either the atrial contribution to forward flow or the peak forward flow velocity was seen in the two groups.

RETROGRADE PULMONARY FLOW

Retrograde flow was seen in the pulmonary artery during early ventricular systole in nine patients. While it was not possible to quantify the amount of retrograde flow, qualitative assessment suggested that the retrograde flow was less appreciable during inspiration.

Discussion

The results of this study are consistent with previously published observations of Doppler flow patterns in the pulmonary artery of patients with an atriopulmonary circulation which suggest that right atrial contraction may contribute to forward flow in the pulmonary artery.[3 10] The addition of simultaneous respirometry, however, provides further information about the determinants of blood flow in the atriopulmonary circulation.

It has been suggested that in the normal circulation the right atrium is at the peak of its work-function curve.[11] Normal inspiration is associated with an increase in right atrial preload[12] and it thus might be expected that inspiration (especially in patients after the Fontan operation in whom the right atrium is operating further along the work-function curve than in normal subjects) would be associated with a reduction in the relative contribution of atrial contraction to pulmonary flow. Our observation that forward flow during atrial contraction is increased by inspiration, suggests that even in patients after the Fontan operation some preload reserve may be maintained by the right atrium. An alternative explanation for these data would be that during inspiration forward flow related to atrial contractility is unchanged but the inspiratory increase in pulmonary forward flow during atrial systole is a manifestation of additional passive flow with the atrium acting as a conduit during inspiration. Perhaps more important is the overall contribution that atrial contraction makes to cardiac output after this operation. Clearly, in the absence of inflow valves, atrial contraction will not only lead to forward flow in the pulmonary artery, but also to retrograde flow into the systemic veins.[10] The lack of a mean pressure rise from systemic veins to pulmonary artery has been suggested as evidence against "effective" pump function of the atrium in the Fontan pulmonary circulation.[6] While there can be no doubt that the atrium is an inefficient pump under these circumstances, a direct extrapolation from pressure measurements to energy state may be somewhat simplistic. Pressure-volume loops from the normal right atrium, clearly show that external work is being imparted to the circulation.[12] The relative proportions of anterograde flow towards the pulmonary circulation and of retrograde flow towards the systemic veins will depend on the relative hydraulic impedence to flow in the pulmonary vascular and the systemic venous beds. A comprehensive assessment of atrial work-function and pulmonary vascular impedence in patients after the Fontan operation is required.

There can be no doubt, however, that the lungs are a potentially important additional source of energy to the Fontan circulation. In our patients a 64% increase in total forward pulmonary flow was seen during normal inspiration. The loss of this augmentation of flow, for example, during positive pressure ventilation, may lead to a significant reduction in cardiac output. Indeed, such a reduction has been shown during the application of low levels of positive end expiratory pressure to patients after the Fontan operation.[13] We have previously shown a considerable effect of respiration on pulmonary blood flow in patients after a total cavopulmonary shunt operation, when there is no atrial chamber interposed between the systemic veins and the pulmonary artery.[7] In these patients it is possible to augment this effect and increase pulmonary blood flow by negative extrathoracic pressure.[8] Based on the results of the present study one might expect a similar effect in patients after atriopulmonary circulation. The potential clinical benefits to patients requiring assisted ventilation after atriopulmonary anastomosis are obvious.

In summary, normal inspiratory effort significantly augments pulmonary blood flow in patients after the Fontan operation. Further studies are required to assess the complex interrelation between atrial preload, atrial contractility, and forward pulmonary blood flow, but it seems that spontaneous respiratory effort is an important additional energy source for pulmonary blood flow in these patients.

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1 Fontan F, Baudet E. Surgical repair of tricuspid atresia *Thorax* 1971;26:240–8.
2 Hurwitt ES, Young D, Escher DJW. The rationale of anastomosis of the right auricular appendage to the pulmonary artery in the treatment of tricuspid atresia. *J Thorac Surg* 1955,30.503–12.
3 Qureshi SA, Richheimer R, McKay R, Arnold R. Doppler echocardiographic evaluation of pulmonary artery flow after modified Fontan operation: importance of atrial contraction. *Br Heart J* 1990,64:272–6.
4 Kreutzer GO, Vargas FJ, Schlichter AJ, *et al* Atriopulmonary anastomosis. *J Thorac Cardiovasc Surg* 1982,83 427–36
5 de Leval MR, Kilner P, Gewillig M, Bull C. Total cavopulmonary connection: a logical alternative to atriopulmonary connection for complex Fontan operations. *J Thorac Cardiovasc Surg* 1988,96.682–95.
6 Bull C Atrial and ventricular dependent circulations In Macartney FJ, ed *Congenital heart disease.* Lancaster. MTP Press, 1986.35–53.
7 Redington AN, Penny D, Shinebourne EA Pulmonary blood flow after total cavopulmonary shunt *Br Heart J* 1991;65.213–7.
8 Penny DJ, Hayek Z, Redington AN The effects of positive and negative extrathoracic pressure ventilation on pulmonary blood flow after the total cavopulmonary shunt procedure. *Int J Cardiol* 1991;30:128–30
9 Nakazawa M, Nakanishi T, Okuda H, *et al* Dynamics of right heart flow in patients after Fontan procedure. *Circulation* 1984;69·306–12.
10 Di Sessa TG, Child JS, Perloff JK, *et al.* Systemic venous and pulmonary arterial flow patterns after Fontan's procedure for tricuspid atresia or single ventricle. *Circulation* 1984, 70·898–902
11 Payne RM, Stone HL, Engleken EJ. Atrial function during volume loading. *J Appl Physiol* 1971;31:326–31
12 Ferguson JJ, Miller MJ, Aroesty JM, Sahagian P, Grossman W, McKay RG. Assessment of right atrial pressure-volume relations in patients with and without an atrial septal defect. *J Am Coll Cardiol* 1989;13.630–6.
13 Williams DB, Kiernan PD, Metke MP, Marsh HM, Danielson GK. Hemodynamic response to positive end-expiratory pressure following right atrium-pulmonary artery bypass (Fontan procedure). *J Thorac Cardiovasc Surg* 1984;87.856–61.

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Abnormal patterns of intraventricular flow and diastolic filling after the Fontan operation: evidence for incoordinate ventricular wall motion

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Abstract

***Objective*—To assess whether regional abnormalities of ventricular function are present in patients after the Fontan operation and to explore the implications of any such abnormalities for ventricular filling.**

***Design and patients*—Prospective study in which 25 patients after the Fontan operation were compared with 25 healthy controls and 12 patients with a univentricular atrioventricular connection, before the Fontan operation.**

***Interventions*—Doppler echocardiography, with simultaneous electrocardiogram, phonocardiogram, and respirometer.**

***Results*—Isovolumic relaxation time was significantly longer in patients after the Fontan operation than in normal children ($p < 0{\cdot}001$) or the preoperative patients ($p = 0{\cdot}001$). Systolic intraventricular flow was detected in 60% of patients after the Fontan operation and in 42% of preoperative patients. After the Fontan operation 80% of patients showed intraventricular flow during isovolumic relaxation compared with 8% of normal children and none of the preoperative patients.**

***Conclusions*—Incoordinate ventricular relaxation is common after the Fontan operation. This may have important implications for ventricular diastolic filling, pulmonary blood flow, and cardiac output in these patients.**

The Fontan operation[1] (atriopulmonary anastomosis), in which a pulmonary circulation devoid of a ventricular pumping chamber is created, has been developed as the definitive method for the palliation of various complex congenital heart lesions. By separating the pulmonary and systemic circulations, arterial oxygenation is improved and systemic ventricular preload is reduced. This operation is palliative rather than curative, however, with a significant late decline in survival and functional state as follow up is extended.[2] The principal cause of this deterioration is circulatory decompensation, but as yet the precise mechanism for this is unclear.

This study of systemic ventricular function in patients after the Fontan operation has principally considered the analysis of ventricular systolic pump function. Many patients display normal or near normal ejection fractions at rest.[3] One longitudinal study showed an improvement in so-called load independent indices of contractility during a seven year follow up.[4] It thus appears unlikely that the late decline in functional state of survivors after the Fontan operation is related to a primary deterioration in ventricular systolic function. It is clear that the study of ventricular function in patients after the Fontan operation must extend beyond the study of systolic pump activity only.

Doppler echocardiography has facilitated the identification of dynamic blood flow patterns in the ventricular cavity during systole[5] and diastole,[6] reflecting the development of transient intraventricular pressure changes secondary to incoordinate ventricular wall motion during ventricular contraction and relaxation. The presence of this intraventricular flow correlates closely with abnormalities of regional wall motion, identified by cineangiography in patients with left ventricular disease.[5 6]

When present during early systole, abnormalities of wall motion may have important implications for overall ventricular efficiency and rate of pressure development,[7] whereas non-uniformity of ventricular wall motion during isovolumic relaxation may slow ventricular pressure decline, resulting in a prolongation of isovolumic relaxation time[8] and a reduction in the rate of ventricular filling during early diastole.[9] So far, regional ventricular wall motion or ventricular diastolic function have not been formally studied in patients after the Fontan operation.

In this study, Doppler echocardiography was used to examine atrioventricular and intraventricular flow patterns in patients before and after the Fontan operation and in healthy controls, so that possible regional abnormalities of ventricular function might be explored.

Methods

PATIENTS

Twenty-five patients (14 male and 11 female) with a median age of 94 (range 12–221 months) were studied at a median interval of 28 (0·03–105) months after the Fontan operation. Fifteen patients had tricuspid atresia (with the ventriculoarterial connection concordant in 13, discordant in one, and double outlet in one). Eight patients had double inlet left ventricle (with the ventriculoarterial connection discordant in six and double outlet in two). One patient had pulmonary atresia with intact interventricular septum and one had double outlet right ventricle with anomalous insertion of the tricuspid valve tensor apparatus precluding a biventricular repair. Fifteen patients had previously undergone insertion of one or more systemic to pulmonary artery shunts, four had undergone pulmonary artery banding alone, two had undergone pulmonary artery banding before insertion of systemic to pulmonary artery shunts, and four had undergone the Fontan operation as a primary operation. Atriopulmonary anastomosis was performed in 22 patients. In two patients the rudimentary ventricle was incorporated into the anastomosis and in one patient a total cavopulmonary anastomosis with an intra-atrial baffle was performed.[10] Indices were compared with 25 age and sex matched controls and 12 patients with a median age of 59 (0·06–258) months and a univentricular atrioventricular connection (eight with absent tricuspid atresia and four with double inlet ventricle) before the Fontan operation. Of these, five had undergone insertion of one or more systemic pulmonary artery shunts and two had undergone pulmonary artery banding.

MEASUREMENTS

Patients were studied at rest, lying in a supine position. Colour flow Doppler echocardiograms were recorded from an apical position, using a 5 MHz or 3·5 MHz transducer interfaced with a Toshiba SSH-160A or Hewlett Packard Sonos 1000 ultrasound machine. The transducer was angled until optimal flow signals were recorded and a pulsed wave, range gated sample volume was positioned at the centre of the colour signal in the inlet of the ventricle, at the level of the tips of the atrioventricular valve leaflets. Simultaneous electrocardiograms, phonocardiograms, and respirometer were recorded. The coincidence of the first and second heart sounds on phonocardiogram, with mitral and aortic valve closure, was verified by M mode echocardiography before measurements were made. All recordings were made at a paper speed of 100 mm/s.

Total electromechanical systole was recorded as time interval between the onset of the QRS complex on the electrocardiogram and the first high frequency component of the second heart sound (Q-A_2). Isovolumic relaxation time was measured as the interval between the first high frequency component of the second heart sound and the onset of early rapid ventricular filling (A_2-E). Peak atrioventricular flow velocity during early diastole (E wave) and during atrial systole (A wave) was measured and the E:A ratio and the E:E + A ratio were measured in each patient.[11 12]

ANALYSIS

Measurements were averaged over three cardiac cycles for all indices; All data are expressed as mean (SD) and the statistical significance of differences between group means was assessed by Student's *t* tests. The null hypothesis was rejected when $p < 0·05$.

Results

TIME INTERVALS

The RR interval was similar in patients after the Fontan operation (708 (141) ms), normal children (704 (139) ms), and in patients with a univentricular atrioventricular connection before the Fontan operation (629 (90) ms). The isovolumic relaxation time, however, was significantly longer in patients after the Fontan operation (93·8 (14·5) ms) than in controls (55·2 (8·6) ms) ($p < 0·0001$) and the preoperative patients (66·4 (22·4) ms) ($p = 0·001$).

ATRIOVENTRICULAR FLOW

Atrioventricular Doppler flow showed early rapid E wave and atrial systolic A wave filling in all patients and controls, except in one patient with a univentricular atrioventricular connection before the Fontan operation, who had summation flow, so that E and A wave filling could not be separated for the purposes of analysis.

The E:A and the E:E + A velocity ratios were similar in patients before and after the Fontan operation (table). The E:A and the E:E + A ratios were higher in the normal children, than in both patient groups, however. The E wave velocity was significantly lower in patients after the Fontan operation than in either the controls or the preoperative patients. In patients after the Fontan operation an inverse relation was observed between isovolumic relaxation time and E wave velocity ($p = 0·007$). Whereas A wave velocity was similar in the control and post operative groups, A wave velocity was significantly higher in patients with a univentricular atrioventricular connection before the Fontan operation.

INTRAVENTRICULAR FLOW

Fifteen of the 25 patients after the Fontan operation (60%) showed the presence of intraventricular Doppler flow during early systole. Twenty patients had diastolic flow during isovolumic relaxation (80%), and 12 displayed both. Intraventricular flow was not detected in two patients after the Fontan operation.

SYSTOLIC INTRAVENTRICULAR FLOW

Systolic intracavitary flow (fig 1), as found in the patients after the Fontan operation, was directed from base to apex and had a mean velocity of 23·7 (5·26) cm/s. This flow began in early systole and persisted for 241·5 (59) ms after the onset of the QRS comlex on the electrocardiogram—that is, 71 (11·2)% of total electromechanical systole. The intraventricular flow during systole was distinct from the atrioventricular flow signal and persisted after atrioventricular valve closure.

A similar pattern was detected during early systole in five of the 12 patients (42%) with a univentricular atrioventricular connection before the Fontan operation. This flow had a mean velocity of 23 (3·46) cm/s and lasted for 237 (65·7) ms after the onset of the QRS complex and was not significantly different from that detected in patients after operation. A lower velocity (15 cm/s) systolic flow, which

Table Atrioventricular velocity profiles and velocity ratios in the three groups of subjects studied. All indices are expressed as mean (SD). The statistical significance of differences between groups was analysed by Student's t test

	Controls	*Pre-Fontan*	*Post-Fontan*	*Control v Pre-Fontan*	*Control v Post-Fontan*	*Pre- v Post-Fontan*
No	25	12	25	—	—	—
RR interval (ms)	704 (141)	629 (90)	708 (141)	NS	NS	NS
E wave velocity (cm/s)	69·9 (18)	65·2 (36·7)	44·8 (17·1)	NS	$p < 0·001$	$p = 0·028$
A wave velocity (cm/s)	29·08 (11·67)	47·8 (23·6)	33·76 (12·6)	$p = 0·003$	NS	$p = 0·025$
E:A ratio	2·6 (0·9)	1·4 (0·4)	1·4 (0·5)	$p < 0·001$	$p < 0·001$	NS
E:E +A ratio	0·71 (0·07)	0·58 (0·07)	0·57 (0·08)	$p < 0·001$	$p < 0·001$	NS
Isovolumic relaxation time (ms)	55·2(8·6)	66·4 (22·4)	93·8 (14·5)	NS	$p < 0·001$	$p = 0·001$

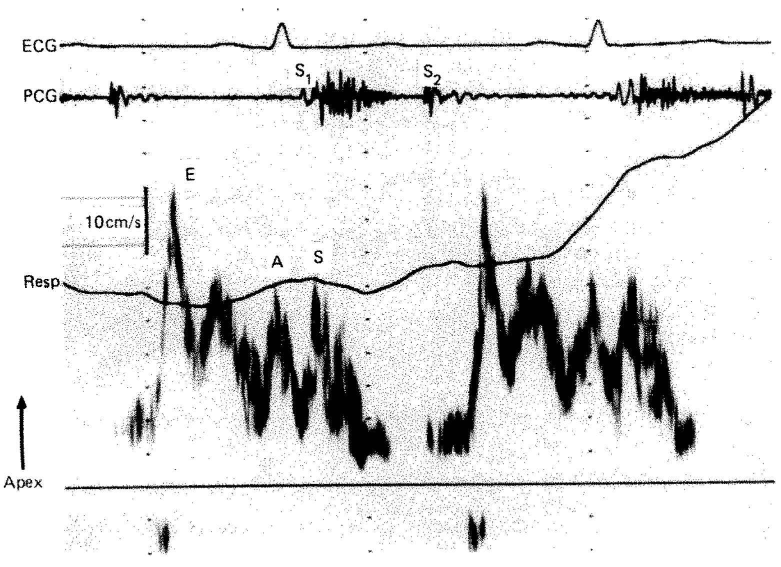

Figure 1 Pulsed wave Doppler velocity tracing with simultaneous electrocardiogram (ECG), phonocardiogram (PCG), and respirometer (RESP) in a patient after the Fontan operation. Base to apex Systolic flow (S) is shown, which begins around the time of the first heart sound on the phonocardiogram (S_1). There is continued atrioventricular flow during mid-diastole (diastasis flow) in this patient.

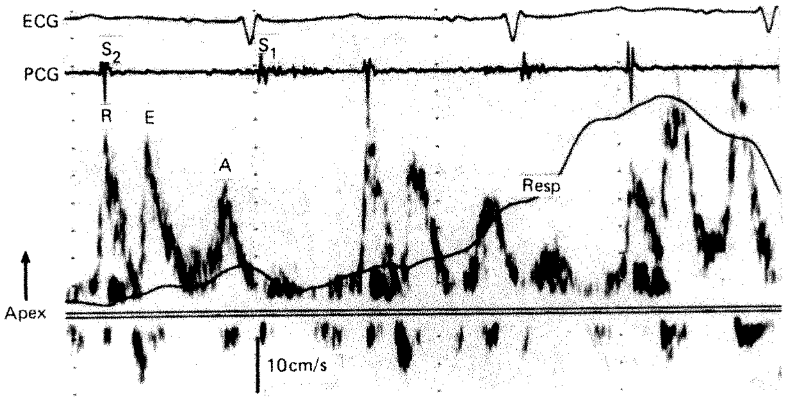

Figure 2 Pulsed wave Doppler velocity tracing in a patient after Fontan operation. Isovolumic relaxation flow (R) peaks at the time of the second heart sound on the phonocardiogram (S_2) and persists until the development of early rapid ventricular filling. ECG, electrocardiogram; PCG, phonocardiogram; Resp, respirometer.

lasted for only 145 ms after the onset of the QRS complex (42% of total electromechanical systole), was detected in two of the 25 normal children.

INTRAVENTRICULAR FLOW DURING ISOVOLUMIC RELAXATION

An early diastolic intraventricular base to apex flow signal was detected in 20 patients after the Fontan operation (80%) (fig 2). This peaked at or just after the time of aortic valve closure, had a mean velocity of 21·4 (6·7) cm/s, and ended with the development of atrioventricular flow. Intraventricular flow with a velocity of 10 cm/s was detected in two normal children (8%), but was not seen in any of the patients with a univentricular atrioventricular connection before the Fontan operation.

There was no relation between the duration of follow up and the presence of abnormal intraventricular flow. Respiration had no significant effect on intraventricular flow.

Discussion

This study shows the presence of two distinct patterns of intraventricular flow in patients after the Fontan operation; the first occurred during early systole and the second during isovolumic relaxation.

SYSTOLIC INTRAVENTRICULAR FLOW

In 15 of 25 patients (60%) an intraventricular Doppler signal, reflecting blood flow towards the apex, occurred in early systole. This was distinct from the atrioventricular flow, and persisted for about 70% of electromechanical systole. A similar signal was seen in five of 12 patients (42%) with a univentricular atrioventricular connection before the Fontan operation, but in only two of 25 normal children. Although the precise mechanism for this flow remains uncertain we postulate that as in other groups of patients with left ventricular disease,[5] it occurs as a result of incoordinate ventricular contraction during early systole.

This hypothesis is supported by the angiographic data of Gibson and coworkers, which showed the presence of delayed onset of ventricular contraction and areas of regional hypokinesis in 11 of 20 patients with a univentricular atrioventricular connection.[13] There was evidence of incoordinate relaxation in only four patients, although this study did not include patients after the Fontan operation.

The aetiology of this systolic incoordination may be related to an alteration in the arrangement of muscle fibres and ventricular geometry resulting from the underlying congenital heart lesion,[14] or from chronic volume overload,[15] or which may be secondary to myocardial necrosis or fibrosis manifest in the myocardium of some patients with congenital heart disease from an ealy age.[14] It is not surprising that the incidence of systolic intraventricular flow is not increased by the Fontan operation, as neither afterload nor global ventricular systolic function seems to be significantly worsened.

INTRAVENTRICULAR FLOW DURING ISOVOLUMIC RELAXATION

By contrast with systolic flow, the incidence of intraventricular flow during isovolumic relaxation was much higher in patients after the Fontan operation (80%) than in the healthy children (89%) and in the children with a univentricular atrioventricular connection before the Fontan operation (0%). Again, the exact mechanism for this phenomenon is unclear, but incoordinate ventricular relaxation may be an explanation. M mode echocardiography studies showed that an acute reduction in ventricular preload precipitated the development of incoordinate left ventricular relaxation in patients with ischaemic heart disease.[8] Furthermore, in patients with left ventricular hypertrophy a similar pattern of base to apex intraventricular flow during isovolumic relaxation was attributed to incoordinate relaxation demonstrated by angiography.[6] By separating the pulmonary and systemic circulations, the Fontan operation imposes an acute and dramatic preload reduction on a previously volume loaded ventricle. Furthermore, our own findings suggest that considerable systemic ventricular "hypertrophy" may develop at the time of the Fontan operation.[16] Presumably this is related to an acute reduction in preload in a ventricle in which shortening fraction and muscle mass remain constant. Indeed in patients studied two months after this operation posterior wall thickness was increased.[4] It thus seems reasonable to postulate that the diastolic flow in patients after the Fontan operation reflects the development of incoordinate ventricular relaxation resulting from an acute preload reduction and the development of a "hypertrophic" left ventricle at the time of operation.

VENTRICULAR RELAXATION AND ATRIOVENTRICULAR FLOW

Incoordinate ventricular relaxation results in an impairment of overall ventricular relaxation with prolonged isovolumic relaxation time,[8] which may cause a reduction in atrioventricular flow velocity during early diastole.[9] In our patients after Fontan operation, the isovolumic relaxation time was prolonged and early atrioventricular filling was lower than in healthy children and patients before operation.

Both E and A wave atrioventricular velocities were proportionately lower in postoperative patients, however, than in patients before the Fontan operation, so that E:A and E:E + A ratios were similar in the two groups. Thus the lower rate of ventricular filling in the patients after operation may merely reflect a reduction in total stroke volume consequent on separation of the systemic and pulmonary circulations. It would be premature to assume that these data provide evidence for changes in ventricular compliance characteristics resulting from the Fontan operation. The inverse relation between isovolumic relaxation time and early filling velocity in these patients suggests that impaired ventricular relaxation may be the primary cause of altered filling after this operation.

This study does provide evidence for the development of incoordinate ventricular relaxation in patients after the Fontan operation. We postulate that the underlying mechanism for these abnormalities is related to a combination of preload reduction and acquired ventricular hypertrophy. The presence of incoordinate ventricular relaxation may alter ventricular diastolic function, which in turn may influence pulmonary blood flow after the Fontan operation. The possible influence of abnormal ventricular relaxation on diastolic filling and cardiac output after the Fontan operation warrant further study.

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1 Fontan F, Baudet E. Surgical repair of tricuspid atresia. *Thorax* 1971,26:240–8.
2 Fontan F, Kirklin JW, Fernandez G, *et al.* Outcome after a "perfect" Fontan operation. *Circulation* 1990;81:1520–36.
3 Hagler DJ, Seward JB, Tajik AJ, Ritter DG. Functional assessment of the Fontan operation combined two-dimensional and Doppler echocardiographic studies. *J Am Coll Cardiol* 1984;4:756–64.
4 Gewillig MH, Lundstrom UR, Deanfield JE, *et al.* Impact of the Fontan operation on left ventricular size and contractility in tricuspid atresia. *Circulation* 1990;81:118–27.
5 Garrahy PJ, Kwan OL, Both DC, DeMaria AN. Assessment of abnormal systolic intraventricular flow patterns by Doppler imaging in patients with left ventricular dyssenergy *Circulation* 1990;82:95–104
6 Sasson Z, Hatle L, Appleton CP, Jewett M, Alderman EL, Popp RL. Intraventricular flow during isovolumic relaxation: description and characterization by Doppler echocardiography. *J Am Coll Cardiol* 1987,10.539–46.
7 Gibson DG. Ventricular function In: Anderson RH, Macartney FJ, Shinebourne EA, Tynan M, eds. *Paediatric cardiology* Edinburgh: Churchill Livingstone, 1987:159–82.
8 Hall RJC, Doran J, Pusey C, McHaffie D, Gibson DG The effect of nitroglycerine, beta-blockade with acebutolol and isometric stress on incoordinate left ventricular function. *Eur Heart J* 1982,3:23–8
9 Appleton CP, Hatle LK, Popp RL. Relation of transmitral flow velocity patterns to left ventricular diastolic funtion: new insights from a combined hemodynamic and Doppler echocardiographic study. *J Am Coll Cardiol* 1988;12: 426–40
10 de Leval MR, Kilner P, Gewillig M, Bull C. Total cavopulmonary connection: a logical alternative to atriopulmonary connection for complex Fontan operations. *J Thorac Cardiovasc Surg* 1988;96.682–95.
11 Mirsky I. Assessment of diastolic function: suggested methods and future considerations. *Circulation* 1984;69: 836–41.
12 Little WC, Downes TR. Clinical evaluation of left ventricular diastolic performance. *Prog Cardiovasc Dis* 1990; 32:273–90.
13 Gibson DG, Traill TA, Brown DJ. Abnormal ventricular function in patients with univentricular heart. *Herz* 1979;4:226–31.
14 Becker AE, Caruso G. Congenital heart disease—a morphologist's view on myocardial dysfunction. In Becker AE, Losekoot TG, Marcelletti C, Anderson RH, eds *Paediatric cardiology vol. 3.* London: Churchill Livingstone, 1981:307–23.
15 Di Donato M, Barletta G, Mori F, Fantini F. Regional left ventricular wall motion abnormalities in chronic volume overload. *Cathet Cardiovasc Diagn* 1983;9:453–62.
16 Penny DJ, Lincoln C, Xiao H, Rigby ML, Redington AN. Acute effects of transition to a Fontan circulation. *Br Heart J* 1991;66:66.

Br Heart J 1991;**66**:379–80

CASE REPORTS

Echocardiographic and angiographic diagnosis of Ebstein's anomaly of the mitral valve

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Abstract

A rare case of Ebstein's anomaly of the mitral valve was diagnosed by cross sectional echocardiography and angiography.

Case report

A black, female child, aged 2 years and 9 months, had presented with a heart murmur when she was 10 days old. When she was one, frequent dyspnoea developed and by the age of two she was in congestive cardiac failure that improved with drug treatment. She was transferred to our hospital nine months later for catheterisation and surgical treatment.

Physical examination showed poor growth and development. The first heart sound was normal and the second heart sound was accentuated. A pansystolic grade 4/6 murmur was heard at the apex and the third heart sound was audible. There was no oedema and the peripheral pulses were normal.

Electrocardiography showed sinus rhythm and evidence of hypertrophy of both the atria and the right ventricle. The chest *x* ray showed considerable cardiomegaly. Cross sectional echocardiography showed that the mitral mural leaflet was displaced downwards, and that much of it adhered to the left ventricular wall. It became free below the level of the tricuspid valve (fig 1). The aortic leaflet of mitral valve also adhered to the left ventricular wall; it too was free below the level of the tricuspid valve.

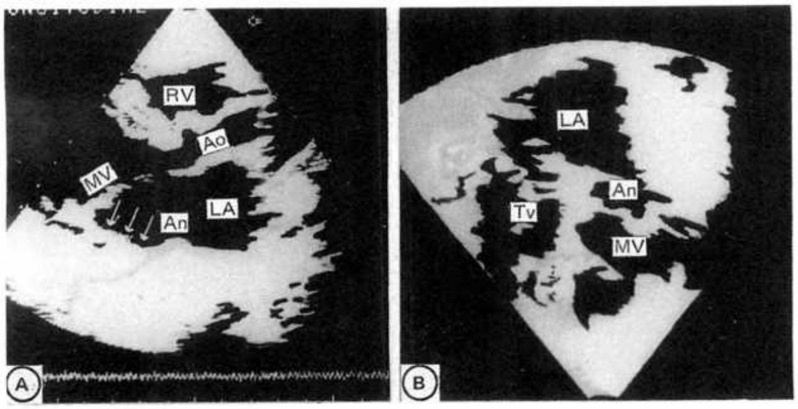

Figure 1 (A) Longitudinal echocardiogram showing the downward displacement of the mitral mural leaflet, much of which adhered to the wall of left ventricle (arrows). Leaflet coaptation of the mitral valve (MV) was displaced downward to the apex of left ventricle. The mitral annulus (An) was in the normal position. The aorta (Ao), left atrium (LA) and right ventricle (RV) are visible. (B) Apical four chamber echocardiogram showing coaptation of mitral leaflets (MV) below the tricuspid valve (Tv) level. The mitral valve annulus (An) was in the normal position, above the tricuspid valve (Tv). The left atrium (LA) was enlarged.

This echocardiographic image suggests discordant atrioventricular connection with the usual atrial arrangement; however, the great arteries were in the normal position. A Doppler study showed severe mitral regurgitation and catheter studies showed pulmonary artery hypertension. Angiocardiography showed that the pulmonary artery arose from an enlarged right ventricle and systolic function of the left ventricle was reduced. The mitral mural leaflet was displaced downwards into the left ventricle. Much of the mural leaflet adhered to the posterior wall of the left ventricle.

There was coaptation of mitral leaflets in systole below the mitral valve annulus near the apex of the left ventricle, which caused functional atrialisation of the proximal part of this ventricle (fig 2).

There was severe mitral regurgitation with dilatation of the left atrium. Ebstein's anomaly of mitral valve was diagnosed and surgery confirmed the features seen at echocardiography and angiocardiography. The mural leaflet was displaced downward and much of it adhered to the ventricular wall; but the wall thickness of the atrialised part of left ventricle was normal and the trabeculae were normal. The mitral leaflets were dysplastic.

The mitral valve was replaced with a IMC-Biomedica bovine pericardium prosthesis. The subsequent course was uneventful.

Discussion

Ebstein's anomaly of mitral valve is a rare malformation first described by Ruschhaupt *et al*[1] and later reported by others.[2 3] Published reports generally describe the necropsy findings.[1 4 5] The embryological origin is obscure.[1]

Adherence of mitral leaflets to the left ventricular walls, which displaces the level of coaptation of the leaflets towards the apex of the ventricle, is described in other reported cases.[2 3 6] In our patient echocardiography identified the downward displacement of mitral mural leaflet. This suggested a discordant atrioventricular connection with usual atrial arrangement; but a more detailed examination showed the normal attachment of the aortic leaflet of the mitral valve. This is the true diagnostic criterion for Ebstein's anomaly

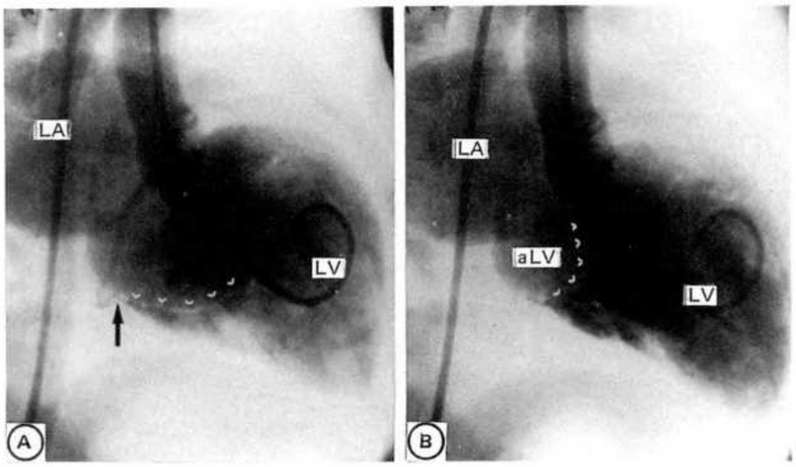

Figure 2 (A) Angiocardiogram of the left ventricle (LV) in diastole (right anterior oblique view) showing downward displacement of mitral mural leaflet (black arrow), and its considerable adherence to the ventricular wall (arrowheads).
(B) Angiocardiographic image of the left ventricle (LV) in systole (right anterior, oblique view) showing downward displacement of mitral leaflet coaptation (arrowheads) and the "atrialised" part of ventricle (aLV). Severe mitral regurgitation and the enlarged left atrium (LA) are also visible.

of the mitral valve.[5] Longitudinal and apical four chamber views gave excellent echocardiographic images of the anatomical features of this anomaly.

The angiocardiographic study confirmed the echocardiographic features and showed the displacement of mitral mural leaflet, its adherence to the ventricular wall, and the atrialisation of the proximal part of the left ventricle. Angiocardiography in right anterior oblique view was very useful in the diagnosis of this malformation, and for evaluation of mitral regurgitation.

There are reported cases of only functional atrialisation of the left ventricle,[2-6] but there is also a report on true anatomical atrialisation of the proximal part of the left ventricle,[1] in which the atrialised part of the ventricle had thin, smooth walls.

In some cases Ebstein's anomaly of the mitral valve was associated with other malformations,[1 4 6] but in our case it was not. Perhaps this was why our patient survived to the age of 2 years and 9 months, and why surgical treatment was successful.

Surgical repair, which is often used for Ebstein's anomaly of the tricuspid valve,[7] could not be used in our patient, because the leaflets were so dysplastic.[7]

Though Ebstein's anomaly of the mitral valve is rare, it must be considered in patients with congenital mitral regurgitation. It is best detected by cross sectional echocardiography and angiocardiographic study.

1 Ruschhaupt DG, Bharati S, Lev M. Mitral valve malformation of Ebstein type in absence of corrected transposition. *Am J Cardiol* 1976;**38**:109–12.
2 Becker AE, Anderson RH. Anomalies of the atrioventricular junction. In: *Cardiac pathology: an integrated text and colour atlas*. London: Churchill Livingstone, 1983:11.29.
3 Anderson RH, Macartney FJ, Shinebourne EA, Tynan M. Mitral valve anomalies and supravalvar mitral ring. In: Anderson RH, Macartney FJ, Shinebourne EA, Tynan M, eds. *Pediatric cardiology*. New York: Churchill Livingstone, 1983:1023–56.
4 Caruso G, Cifarelli ABG, Facilome F. Ebstein's malformation of the mitral valve in atrioventricular and ventriculoarterial concordance. *Pediatr Cardiol* 1987;**8**:209–10.
5 Leung M, Rigby ML, Anderson RH, Wyse RKH, Macartney FJ. Reversed offsetting of the septal attachments of the atrioventricular valves and Ebstein's malformation of the morphologically mitral valve. *Br Heart J* 1987;**57**:184–7.
6 Dusmet M, Oberhaensli I, Cox JN. Ebstein's anomaly of the tricuspid and mitral valves in an otherwise normal heart. *Br Heart J* 1987;**58**:400–4.
7 Danielson GK, Fuster V. Surgical repair of Ebstein's anomaly. *Ann Surg* 1982;**196**:499–504.

Br Heart J 1991;**66**:381–3

Double outlet left ventricle: diagnosis with magnetic resonance imaging

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Abstract

A complex congenital cardiac malformation in a female patient was evaluated several times by angiocardiography and echocardiography in childhood but a definite diagnosis was not established. Segmental analysis of the heart and the great vessels by magnetic resonance imaging when the patient was 34, however, showed a double outlet left ventricle in which the aorta was situated anterior to and to the left of the pulmonary trunk and an associated subaortic ventricular septal defect with pulmonary valve stenosis.

This is the first time that this extremely rare cardiac malformation has been diagnosed by magnetic resonance imaging.

Double outlet left ventricle is a rare (incidence less than 1 in 200 000[1]) congenital cardiac malformation in which the aorta and the pulmonary trunk both arise entirely or predominantly above the morphologically left ventricle. Eighteen cases of the type described in this paper have been reported.[2]

Magnetic resonance imaging is a valuable, non-invasive tool for the visualisation of the anatomy of the heart, especially when complex cardiac malformations are suspected.[3] It can also be used to perform segmental analysis[4] to define atrial situs, atrioventricular connections, ventricular morphology, ventriculoarterial connections, the position of the great arteries, and associated defects. We describe the use of magnetic resonance imaging in a case of double outlet left ventricle in which a definite diagnosis was never established despite extensive echocardiographic and angiocardiographic examination.

Case report

This female patient presented with asphyxia and frequent attacks of mild cyanosis shortly after birth and was examined by angiocardiography at the age of 11 years (we have no information on earlier examinations). The diagnosis at the time was a double outlet right ventricle of the Taussig-Bing type associated with a ventricular septal defect.

At the age of 15 years she complained of fatigue during moderate exercise. Physical examination showed moderate cyanosis, cardiomegaly, a pansystolic murmur 3/6 at the apex, and an ejection type murmur 5/6 over the second left intercostal space. The electrocardiogram showed right axis deviation and a right bundle branch block pattern. The chest *x* ray showed an enlarged heart, a narrow vascular pedicle, and pulmonary plethora. A ventricular septal defect with right to left shunting and pulmonary stenosis was suspected. She was recatheterised and the suspected findings were confirmed. The origin of the aorta was shown to be anterior and to the left of the origin of the pulmonary trunk. Oxygen saturation was higher in the pulmonary artery (84%) than in the aorta (77%). Surgical correction was not advised at the time because the symptoms were mild.

Echocardiography when she was 32 reconfirmed the results of angiocardiography, but a definite diagnosis could not be established. At the age of 34, cyanosis had slightly increased and the patient was referred to our hospital for magnetic resonance imaging of the heart and great vessels. Spin echo acquisitions were performed in the three orthogonal planes with a 1·5 T imager (Philips Gyroscan). The study was continued with a sagittally oriented gradient (cine) echo acquisition in the plane through the ventricular septal defect to visualise shunt flow and left ventricular outflow. Segmental analysis was used to identify atrial situs, ventricular morphology, atrioventricular connections, ventriculoarterial connections, position of the great arteries, and associated defects.

SITUS

The bronchial anatomy seen on conventional

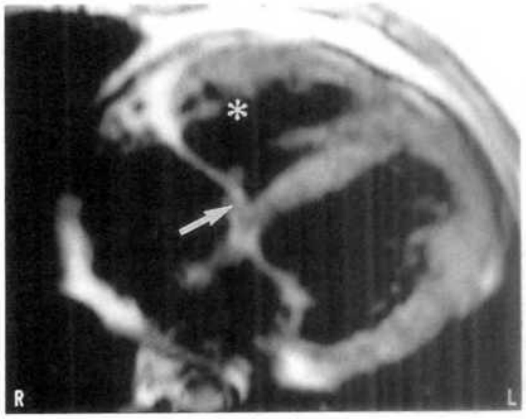

Figure 1 Magnetic resonance image of an axial slice at midventricular level shows the slightly more apical attachment of the tricuspid valve to the septum (arrow) and the coarser trabeculation of the anterior ventricle (asterisk), indicating a morphologically right ventricle. The muscular infundibulum was identified in a more cephalad section.

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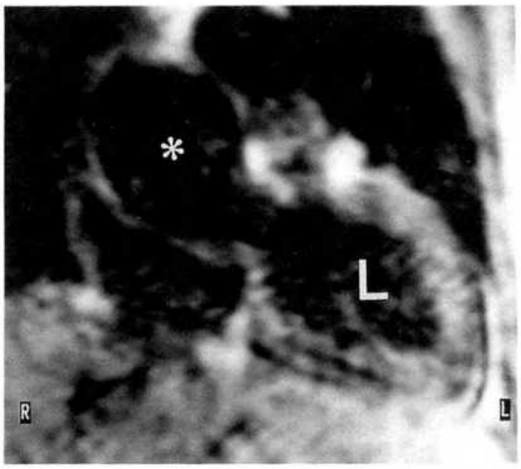

Figure 2 Magnetic resonance image of a coronal slice through the posterior morphologically left ventricle (L), showing the connection with the severely dilatated pulmonary trunk (asterisk).

radiography indicated situs solitus of the atria. This was confirmed by identification of the atrial appendages and the location of the inferior vena cava, abdominal aorta, liver and stomach on a coronal magnetic resonance imaging series. Both venae cavae drained normally into the right atrium.

ATRIOVENTRICULAR CONNECTIONS
Axial slices showed that the anteriorly situated ventricle was the morphologically right ventricle, in view of the thick muscular outflow tract, the trabecular pattern, and the more apical septal slip attachment of the tricuspid valve to the septum compared with the mitral valve. Moreover, there were two atria, each draining into their own ventricle (fig 1). The total picture was one of biventricular concordant atrioventricular connections.

VENTRICULOARTERIAL CONNECTIONS
The coronal slices clearly showed a dilated pulmonary trunk originating from the posterior (morphological left) ventricle (fig 2). The left sided aorta was connected with the infundibulum of the anterior ventricle, straddling the ventricular septum in such a way that most of the aorta arose above the left ventricle. This indicated that the patient had a double outlet left ventricle.

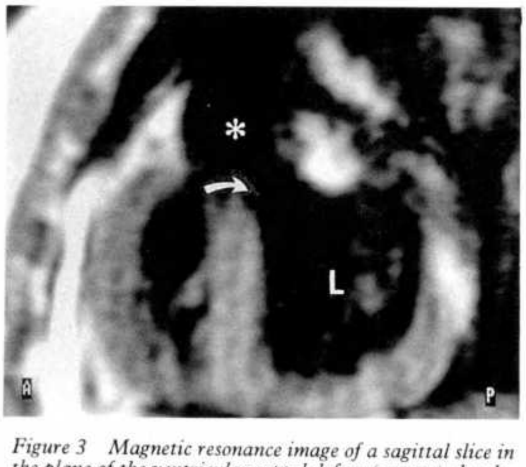

Figure 3 Magnetic resonance image of a sagittal slice in the plane of the ventricular septal defect (arrow) clearly showing the relation of the aorta (asterisk) to the defect, resulting in the posterior, morphologically left ventricle (L) being the main source of aortic blood supply.

POSITION OF THE GREAT ARTERIES
The origin of the pulmonary trunk was located to the right, caudal, and posterior of the aortic origin—a situation which is often seen in congenitally corrected (discordant atrioventricular connections) transposition. A subaortic muscular infundibulum was identified together with pulmonary-mitral fibrous continuity.

ASSOCIATED DEFECTS
A defect of the atrial septum was found within the region of the oval fossa.[5 6] The ventricular septal defect was clearly visualised in the sagittal plane (fig 3). The location was subaortic, resulting in the aorta being supplied mainly by the morphological left ventricle.

FUNCTIONAL EVALUATION
Cine magnetic resonance imaging, especially in the movie mode, showed diastolic right to left shunting and systolic flow from the left ventricle into the aorta.

Segmental analysis performed with magnetic resonance imaging indicated a diagnosis of double outlet left ventricle in which the origin of the aorta lay anterior and left from the origin of the pulmonary trunk together with severe dilatation of the pulmonary trunk (consistent with the pulmonary valve stenosis found at echocardiography), a subaortic ventricular septal defect with right to left shunting, and an atrial septal defect within the region of the oval fossa.

Discussion

Double outlet ventricles with biventricular arterioventricular connections account for about 1% of all cases of congenital heart disease and the left ventricle is affected in less than 5% of these cases.[2] Over 100 cases of double outlet left ventricle have been reported since 1967.[2 7] Before then this anomaly was regarded as being embryologically impossible.[8] Until recently this complex malformation could be examined only by angiocardiography.[9] In our patient surgical intervention was postponed because cyanosis was mild and the anatomical diagnosis was uncertain. Because of the patient's increasing fatigue and cyanosis magnetic resonance imaging was performed to elucidate the anatomy and haemodynamic function.

Surgical correction is often achieved by closing the ventricular septal defect, disconnecting the pulmonary trunk from the left ventricle, and re-establishing the connection between the right ventricle and pulmonary trunk through an external conduit. In some cases a Fontan-type correction may be preferred. Even intraventricular rerouting can be performed occasionally.[9] The development of pulmonary arterial hypertension, however, may limit the surgical options. When a final diagnosis cannot be established with the conventional methods, magnetic resonance imaging can be of great value in the analysis of complex congenital malformations of the heart, as is shown in this case of a very rare cardiac malformation.

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1 Wilkinson JL. Double outlet ventricle. In: Anderson RH, Macartney FJ, Shinebourne EA, Tynan M, eds *Paediatric cardiology, vol 2.* Edinburgh: Churchill Livingstone, 1987 889–911.

2 Van Praagh R, Weinberg PM, Srebro JP. Double outlet left ventricle. In Adams FH, Emmanouilides GL, Riemenschneider TA, eds. *Moss' heart disease in infants, children and adolescents.* Baltimore: Williams and Wilkins, 1989. 461–73.

3 Kersting-Sommerhoff BA, Diethelm L, Stanger P, *et al.* Evaluation of complex congenital ventricular anomalies with magnetic resonance imaging. *Am Heart J* 1990, 120.133–42.

4 Guit GL, Bluemm R, Rohmer J, *et al.* Levotransposition of the aorta: identification of segmental cardiac anatomy using MR imaging. *Radiology* 1986;161:673–9

5 Dinsmore RE, Wismer GL, Guyer D, *et al.* Magnetic resonance imaging of the interatrial septum and atrial septal defects. *AJR* 1985,145.697–703.

6 Diethelm L, Déry R, Lipton MJ, Higgins CB. Atrial-level shunts sensitivity and specificity of MR in diagnosis *Radiology* 1987;162·181–6.

7 Otero Coto E, Quero Jimenez M, Castaneda AR, Rufilanchas JJ, Deverall PB. Double outlet from chambers of left ventricular morphology. *Br Heart J* 1979;42 15–21.

8 Van Mierop LHS, Wiglesworth FW Pathogenesis of transposition complexes. II Anomalies due to faulty transfer of the posterior great artery *Am J Cardiol* 1963;12:226–32.

9 Brandt PWT, Calder AL, Barrat-Boyes BG, Neutze JM. Double outlet left ventricle. Morphology, cineangiocardiographic diagnosis and surgical treatment. *Am J Cardiol* 1976;38.879–909

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EPIDEMIOLOGY

Physical activity and ischaemic heart disease in middle-aged British men

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Abstract

***Objective*—To assess the relation between reported physical activity and the risk of heart attacks in middle aged British men.**

***Design*—Prospective study of middle-aged men followed for a period of eight years (The British Regional Heart Study).**

***Setting*—One general practice in each of 24 British towns.**

***Participants*—7735 men aged 40–59 years at initial examination.**

***End point*—Heart attacks (non-fatal and fatal).**

***Measurements and main results*—During the follow up period of eight years 488 men suffered at least one major heart attack. A physical activity score used was developed and validated against heart rate and lung function (FEV_1) in men without evidence of ischaemic heart disease. Risk of heart attack decreased significantly with increasing physical activity; the groups reporting moderate and moderately vigorous activity experienced less than half the rate seen in inactive men. The benefits of physical activity were seen most consistently in men without pre-existing ischaemic heart disease and up to levels of moderately vigorous activity. Vigorously active men had higher rates of heart attack than men with moderate or moderately vigorous activity. The relation between physical activity and the risk of heart attack seemed to be independent of other cardiovascular risk factors. Men with symptomatic ischaemic heart disease showed a reduction in the rate of heart attack at light or moderate levels of physical activity, beyond which the risk of heart attack increased. Men with asymptomatic ischaemic heart disease showed an increasing risk of heart attack with increasing levels of physical activity, but with a progressive decrease in case fatality. Overall, men who engaged in vigorous (sporting) activity of any frequency had significantly lower rates of heart attack than men who reported no sporting activity. However, when all men reporting regular sporting activity at least once a month were excluded from analysis, there remained a strong inverse relation between physical activity and the risk of heart attack in men without pre-existing ischaemic heart disease.**

***Conclusion*—This study suggests that the overall level of physical activity is an important independent protective factor in ischaemic heart disease and that vigorous (sporting) exercise, although beneficial in its own right, is not essential in order to obtain such an effect.**

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There is considerable evidence that increased levels of physical activity are associated with lowered incidence rates of ischaemic heart disease.[1] Particular attention has been paid to leisure time activity because few middle-aged men do physically demanding work and because, in public health terms, occupational activity is not amenable to change. Studies in British civil servants suggest that exercise is associated with a reduced risk of coronary events only when the exercise is both vigorous and sustained.[2-4] This raises the important issue of whether lesser levels of physical activity have any effect on diminishing the risk of heart attack, an issue of considerable importance in a society in which regular vigorous activity is exceptional. Studies in the United States suggest that there is a continuous relation between physical activity and protection from heart attack.[5-7] It has been suggested that this beneficial effect is largely mediated by the effects of physical activity on known coronary risk factors.[8] In most studies, the relation has been examined in people free of clinical evidence of ischaemic heart disease and little is known about the long term effects of exercise in people with pre-existing evidence of ischaemic heart disease. The present paper examines the relation between physical activity and risk of heart attack in middle-aged men, drawn from general practices in 24 British towns, which are representative of the socioeconomic distribution of men in Great Britain. It includes men with pre-existing ischaemic heart disease.

Subjects and methods

The British Regional Heart Study is a large prospective study of cardiovascular disease comprising 7735 men aged 40–59 selected from age-sex registers of one group general practice in each of 24 towns in England, Wales, and Scotland. The criteria for selecting the town, the general practice, and the subjects as well as the methods of data collection have been reported.[9] Research nurses administered to each man a standard questionnaire that included questions on smoking habits, alcohol intake, physical activity, and medical history. Several physical measurements were made and blood samples were taken for measurement of biochemical and haematological variables. Details of the measurement of serum lipid concentrations have been described.[10] The men were classified according to their current smoking status into five groups: those who had never smoked, ex-cigarette smokers, and three groups of current smokers (<20, 20, >20 cigarettes/day). Those who had only ever smoked pipe/cigars were grouped as "never smoked". Ex-cigarette smokers who currently smoked pipe/cigars were grouped as ex-cigarette smokers. Alcohol consumption was recorded using questions on frequency, quantity, and type, similar to those used in the 1978 General Household Survey. Heavy drinkers were defined as those who regularly drank more than six drinks a day. The longest-held occupation of each man was recorded, and the men were grouped into one of six of the Registrar General's social classes: I, II, III non-manual, III manual, IV, and V. Men who had spent most of their working life in the armed forces form a separate group. For some analyses social classes I, II, and III non-manual were combined as non-manual workers and social classes III manual, IV, and V as manual workers. Body mass index calculated as weight/height^2 was used as an index of relative weight. Each man was weighed in trousers and socks to the nearest 0·1 kg on an MPS110 field survey scale and height was measured without shoes to the nearest millimetre with a Harpenden Stadiometer with digital meter. Obesity was defined as ≥ 28 kg/m^2, which represents the top 20% of the body mass index distribution in these men. Heart rate was determined from the electrocardiogram. Forced expiratory volume in one second (FEV$_1$) was measured by a Vitalograph spirometer (model J49–B2) with the subject seated. Two consecutive readings were made 15 seconds apart and the maximum of these two readings was used. The FEV$_1$ values used in this paper are height standardised to 1·73 m, the average height of the men in this study.

BREATHLESSNESS

A modified version of the Medical Research Council Questionnaire on Respiratory Symptoms (1966 version) was administered at the initial examination. Each man was asked: (*a*) Do you get short of breath walking with people your own age on ground level? (*b*) On walking up hills or stairs, do you get more breathless than people your own age? (*c*) Do you ever have to stop walking because of breathlessness? Each affirmative answer scored 1, giving a possible score of 0–3. Those who scored ≥ 1 were defined as those reporting symptoms of breathlessness.

Table 1 Type and duration/frequency of physical activity with assigned scores and number of men

Activity	*Score*	*n*
Regular walking		
None	0	4459
≤20 min/weekday	1	822
21–40	2	941
41–60	3	717
61–90	4	162
>90	5	79
Recreational activity		
Very inactive	0	333
Fairly inactive	1	906
Average (4 h/weekend)	3	2478
Fairly active	5	2086
Very active	7	1899
Cycling:		
None	0	6759
≤15 min/day	2	64
16–30	4	233
31–45	6	110
46–60	8	68
>1 h	10	23
Sporting activity		
None	0	4722
Occ (<1 mnth)	2	894
1–3 times/mnth	4	390
4–7	8	764
8–11	12	421
12–15	16	233
16–19	20	93
≥20	24	190

These categories are not mutually exclusive

PRE-EXISTING ISCHAEMIC HEART DISEASE

The prevalence of ischaemic heart disease was measured in three ways at initial examination.

(*a*) The men were asked whether a doctor had ever told them that they had angina or myocardial infarction (heart attack, coronary thrombosis).

(*b*) The WHO (Rose) chest pain questionnaire for angina or possible myocardial infarction was administered to all men at the initial examination.[11]

(*c*) A three orthogonal lead electrocardiogram was recorded at rest and analysed by computer in the Department of Medical Cardiology, Glasgow Royal Infirmary.

The men were separated into three groups according to the degree of evidence of ischaemic heart disease present at screening.

(A) No evidence of ischaemic heart disease on WHO (Rose) chest pain questionnaire, electrocardiogram, or recall of a doctor diagnosis of ischaemic heart disease (n = 5767).

(B) Men with evidence suggesting ischaemic heart disease short of a definite myocardial infarction. This group contains those with electrocardiographic evidence of possible myocardial infarction and definite or possible myocardial ischaemia, those with angina or a possible myocardial infarction on WHO chest pain questionnaire, or those with recall of a doctor-diagnosis of angina (n = 1515).

(C) Men with evidence of a previous definite myocardial infarction on electrocardiogram or who recalled a doctor diagnosis of a heart attack (n = 428).

In the subsequent analyses men in groups B and C are regarded as having pre-existing ischaemic heart disease.

PHYSICAL ACTIVITY

The men were asked to indicate their usual pattern of physical activity, under the headings of regular walking or cycling, recreational activity, and sporting (vigorous) activity. A physical activity (exercise) score was derived for each man based on the frequency and type (intensity) of the physical activity. Scores were assigned for each type of activity and duration based on the intensity and energy demands of the activities reported (table 1). This was based on the recommendations of a National Heart, Lung and Blood Institute (NHLBI) workshop[12] and the Minnesota intensity codes.[13] Scores were heavily weighted on vigorous exercise. Physical activity at work was excluded from the score partly because few middle-aged men do physically demanding work and partly because such activity is not readily amenable to modification. Though the gradings were arbitrary we tried to ensure that any given score implied approximately equal intensity and energy demands for the various types of activity. The total score for each man was not a measure of total time spent in physical activity but was a relative measure of how much physical activity has been carried out or energy expended. Regular walking and cycling related to weekday journeys, including those to and from work. Recreational activity includes gardening, pleasure walking, and do-it-yourself jobs. Sporting (vigorous) activity includes running, golf, swimming, tennis, sailing, digging, etc. It was not possible to identify the type of vigorous activity for each man (copies of the questionnaire are available on request) but it was regarded as being vigorous.

PHYSICAL ACTIVITY INDEX

The men were grouped into six broad categories based on their total score.

0–2 *Inactive* (n = 686).
3–5 *Occasional* (n = 2345). Regular walking or recreational activity only.
6–8 *Light* (n = 1761). More frequent recreational activities or vigorous exercise less than once a week.
9–12 *Moderate* (n = 1205). Cycling or very frequent recreational activities or sporting activity once a week.
13–20 *Moderately vigorous* (n = 1120). Sporting activity at least once a week or frequent cycling, plus frequent recreational activities or walking; or frequent sporting activity only.
≥21 *Vigorous* (n = 513). Very frequent sporting exercise or frequent sporting exercise plus other recreational activities.

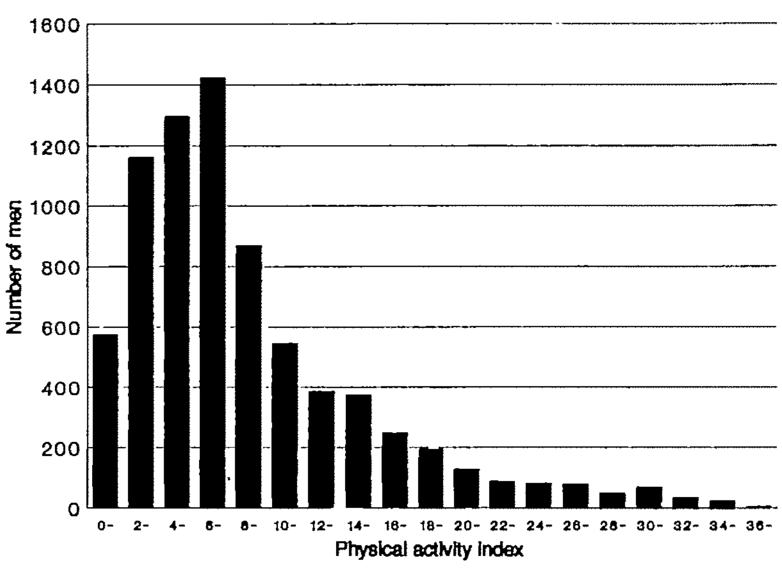


Figure 1 Distribution of physical activity index in 7630 men.

FOLLOW UP

All men, whether or not they showed evidence of ischaemic heart disease at initial examination, were followed up for all cause mortality and cardiovascular morbidity. Information on death was collected through the established "tagging" procedures provided by the National Health Service registers in Southport (England and Wales) and Edinburgh (Scotland). Major ischaemic heart disease events (fatal and non-fatal) were based on an eight year period of follow up for all men. A non-fatal myocardial infarction was diagnosed according to WHO criteria. Fatal events were defined as death from ischaemic heart disease (International Classification of Disease 9th revision: codes 410–414) as the underlying cause. They comprised any ischaemic heart disease death in an individual during the eight year follow up irrespective of a previous non-fatal event during that period. Case fatality was defined as the proportion of the major ischaemic heart disease events in which death occurred during the first event during follow up and within 28 days and in which the death certificate recorded ischaemic heart disease (ICD codes 410–414).

STATISTICAL METHODS

Multiple logistic regression was used to obtain the rates adjusted for age, smoking, body mass index, and social class and the relative risks adjusting additionally for breathlessness, high density lipoprotein-cholesterol, total cholesterol, and systolic blood pressure. Age, body mass index, high density lipoprotein-cholesterol, total cholesterol, systolic blood pressure were fitted as continuous variables, physical activity as five dummy variables, smoking as four dummy variables (never, ex-, light, moderate and heavy), social class as two dummy variables (manual, non-manual and armed forces) and breathlessness as three dummy variables (none, light, moderate and severe). Tests for trend were assessed by assigning quantitative values 1–6 for the six groups of physical activity and fitting physical activity as a continuous variable rather than as five dummy variables.

Results

Within the eight year follow up there were 488 major ischaemic heart disease events ("heart attacks") (fatal 217 and non-fatal 271). The physical activity total score was available for 7630 men. Some men did not provide details on all the components that contributed to the score (n = 105, including six who experienced a heart attack) and they have been excluded from analyses that use the total score. The total score

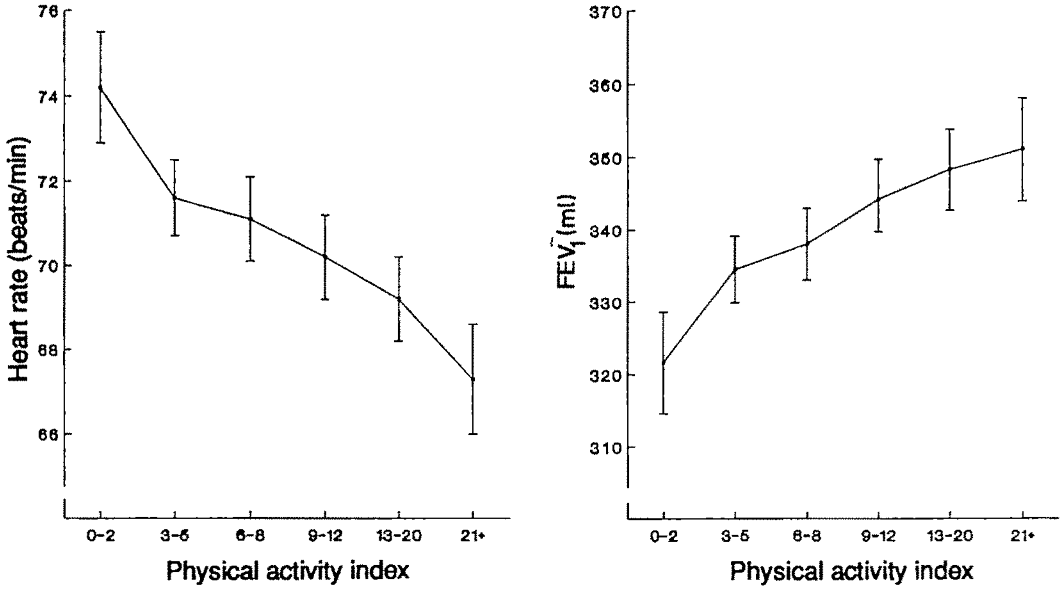


Figure 2 Mean heart rate and FEV_1 according to physical activity index in 5714 men with no evidence of ischaemic heart disease. Means adjusted for age, body mass index, social class, and smoking status.

ranged from 0 to 41 with a median of 7. Figure 1 shows the distribution of the score.

VALIDITY OF THE SCORE

It is well established that regular exercise improves physical fitness and lowers heart rate. Because heart rate is strongly influenced by the presence of pre-existing heart disease we examined the association between physical activity and heart rate in men with no evidence of ischaemic heart disease (fig 2). There was a strong association between physical activity and heart rate even after adjusting for age, body mass index, social class, and smoking, with heart rate decreasing significantly with increasing activity ($p < 0{\cdot}0001$).

FEv$_1$ was also considered as a possible method of validating the physical activity index and it increased progressively with increasing physical activity ($p < 0{\cdot}0001$), even after adjusting for age, body mass index, social class, and smoking (fig 2). However, although ventilatory capacity is related to recreational activity, it is poorly correlated with other measures of physical fitness[14] and validation in this study rests on the relation with heart rate.

PHYSICAL ACTIVITY AND HEART ATTACK

Figure 3 shows the crude and age adjusted heart attack rates for all men in the study separated into the six physical activity categories. Men who were inactive had a significantly higher attack rate than all other men and risk decreased significantly with increasing activity ($p < 0{\cdot}001$). The apparent benefit of physical activity was most clearly seen in those who did moderate to vigorous activities (score $\geqslant 9$). These men had more than a 50% reduction in the risk of heart attack compared with men who were inactive.

PHYSICAL ACTIVITY AND PERSONAL CHARACTERISTICS

Because physical activity is known to be associated with other health related behaviours and is also conditioned by ill health, we examined the personal characteristics and prevalence of ischaemic heart disease in the six physical activity categories (table 2). Those who were moderately active or more (score $\geq$ 9) tended to be younger and were more likely to be non-manual workers. There was little difference in age and social class between those who were inactive (0–2) and men who were occasionally or lightly active (score 3–8). The proportion of current smokers decreased with increasing physical activity. The proportion of ex-smokers was similar in all groups. The proportion of men who had never smoked was highest in the most active group and decreased considerably towards those who are inactive. The proportion of obese men decreased progressively with increasing activity even though the mean body mass index only decreased slightly. Inactive men were more likely to be heavy drinkers (> 6 drinks daily)

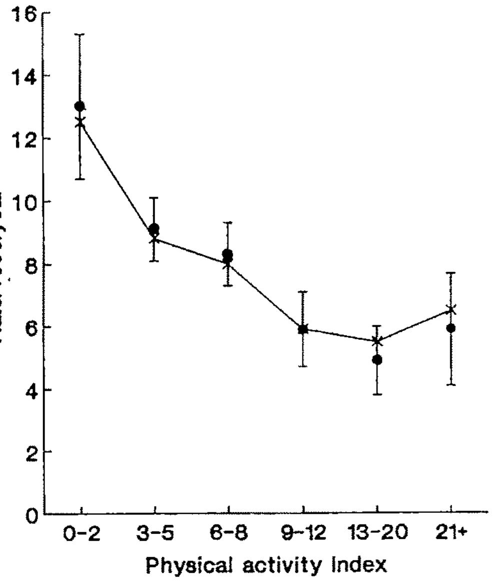


Figure 3 Heart attack rates (per 1000/year) according to physical activity index. Crude rates (●) with 95% confidence intervals and age adjusted rates (×).

Table 2 Personal characteristics and prevalence of ischaemic heart disease and breathlessness according to physical activity score

	Physical activity index					
	0–2	*3–5*	*6–8*	*9–12*	*13–20*	*21+*
No of men (%)	686 (9)	2345 (31)	1761 (23)	1205 (16)	1120 (15)	513 (7)
No. IHD events	71	171	116	56	44	24
Age						
Mean	50·9	50·8	50·6	50·1	48·8	49·0
SE	(0·22)	(0·12)	(0·14)	(0·17)	(0·17)	(0·26)
% 55–59	29	28	28	27	18	20
% Manual	67	66	64	58	47	42
% Smoker.						
Current	53	44	44	40	29	28
Ex	32	35	33	35	38	39
Never	15	19	23	25	33	33
Mean BMI·	25·8	25·7	25·4	25·3	25·4	25·0
SE	(0·15)	(0·07)	(0·08)	(0·09)	(0·08)	(0·12)
% Obese	25	22	19	16	17	13
% Heavy drinkers	16	11	21	9	9	9
% IHD (any):	36	27	26	23	20	16
%angina (Q) or recall of angina (DR)	25	16	15	12	10	7
% MI (ECG/DR)	8·8	6·8	5·1	4·8	3·9	2·2
Breathlessness:						
% Any	36·9	21·4	17·0	12·0	7·6	5·3
%Severe	12·3	4·3	2·5	2·1	1·0	0·2

BMI, body mass index; DR, recall of doctor diagnosis, ECG, on electrocardiogram; IHD, ischaemic heart disease; MI, myocardial infarction, Q, on WHO (Rose) questionnaire.

but there was little difference between the other activity groups. There was a strong association between physical activity and presence of pre-existing ischaemic heart disease, the prevalence tending to decrease with increasing physical activity. Those who were inactive had the highest prevalence of angina. The proportion of men with definite myocardial infarction decreased steadily as physical activity increased. The proportion of men reporting any degree of breathlessness, in particular severe breathlessness, decreased considerably with increasing activity. This is likely to be associated with both the high prevalence of ischaemic heart disease as well as the lack of physical fitness.

PHYSICAL ACTIVITY, AGE, AND HEART ATTACK

The relation between physical activity and risk of heart attack was examined separately in those aged 40–49 and 50–59 after adjustment for smoking, social class, and body mass index (fig 4). In the older men being inactive was associated with a high rate of heart attack, suggesting the effect of pre-existing ischaemic heart disease. In younger men, those who were inactive had rates similar to occasionally or lightly active men. However, in both age groups moderate (9–12) to moderately vigorous (13–20) activities were associated with lower rates than inactive or occasionally active men. In younger men, those who were most active had a risk similar to the inactive, occasional, or lightly active men. In these men the risk of heart attack was significantly higher ($p = 0·03$) than in the moderately vigorous men. This was not seen for older men, and may reflect random variation or the type of sport undertaken. In these younger vigorously active men there was no undue increase in the proportion of sudden death.

PHYSICAL ACTIVITY AND PRE-EXISTING ISCHAEMIC HEART DISEASE

Because the presence and severity of ischaemic heart disease is likely to condition patterns of physical activity, we examined the relation separately in men with and without ischaemic heart disease, adjusting for age, social class, body mass index, and smoking (fig 5). In men without pre-existing ischaemic heart disease there was a strong inverse association between physical activity and heart attack up to levels of moderately vigorous activity ($p < 0·001$). Those who were occasionally or lightly active showed a small decrease in risk of heart attack compared with inactive men. Those engaged in moderate or moderately vigorous activity had more than a 50% reduction in risk of heart attack compared with inactive men. The vigorously active men had a significant increase in risk compared with those who were engaged in moderate or moderately vigorous activity ($p = 0·03$). Because breathlessness has also

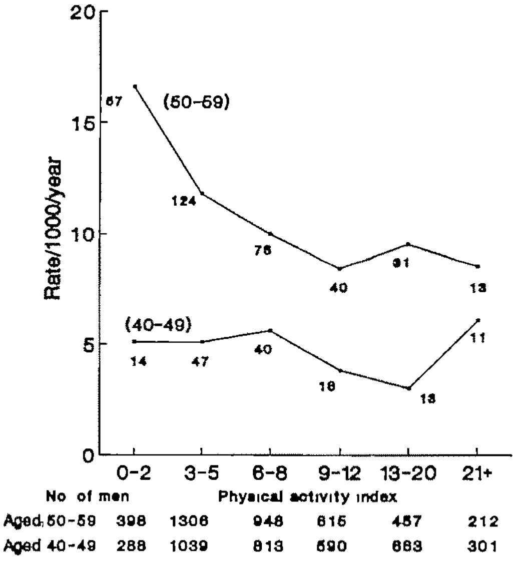
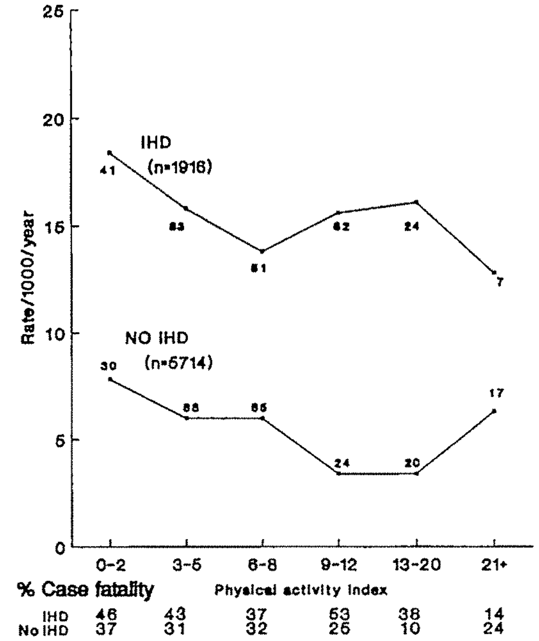


Figure 4 Heart attack rate (per 1000/year) in men aged 40–49 and 50–59 years according to physical activity index. Adjusted for body mass index, social class, and smoking. Number of heart attack events indicated on figure.



% Case fatality

	0-2	3-5	6-8	9-12	13-20	21+
IHD	46	43	37	53	38	14
No IHD	37	31	32	26	10	24

Figure 5 Heart attack rates (per 1000/year) according to physical activity index in men with and without evidence of ischaemic heart disease. Adjusted for age, body mass index, social class and smoking. Number of heart attacks indicated on figure.

been shown to be a predictive factor for ischaemic heart disease[15] and is strongly associated with physical activity (table 2) we examined the relation after adjusting for breathlessness as well. This made little difference to the association seen. Even exclusion of all men with any grade of breathlessness (n = 719) made no difference to the pattern seen in fig 5. Case fatality decreased as physical activity increased, with the lowest case fatality in the moderately vigorous men. It rose again in the vigorously active men.

In men with pre-existing ischaemic heart disease, inactive men showed the highest risk of heart attack but thereafter there was no consistent pattern in the risk of heart attacks with increasing levels of physical activity.

SYMPTOMATIC AND ASYMPTOMATIC ISCHAEMIC HEART DISEASE

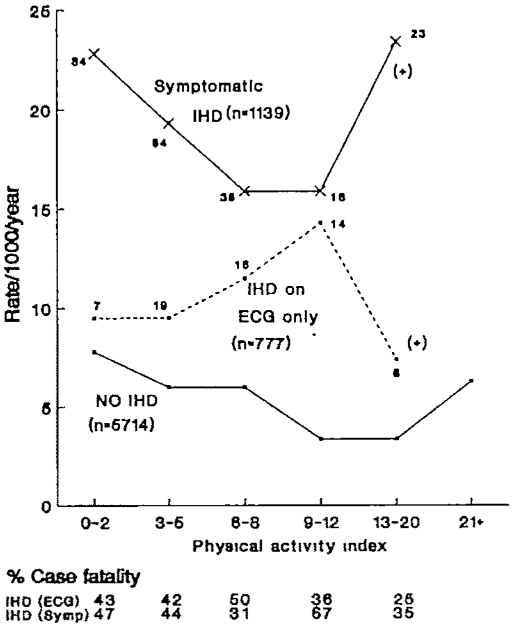
The apparent absence of clear benefit from physical activity in men with pre-existing ischaemic heart disease may partly be due to men having modified their exercise pattern as a consequence of developing ischaemic heart disease. A few may increase their activity in an attempt to lower their risk of major events, but most are likely to decrease their physical activity because of chest pain or breathlessness. Physical exertion may also have different effects on people with various manifestations of ischaemic heart disease. We examined these possibilities further by dividing the 1916 men with evidence of ischaemic heart disease into two groups—those with objective measurements of ischaemic heart disease only (that is, those who did not report any chest pain but had ischaemic electrocardiographic abnormalities (asymptomatic) and those who reported angina or possible myocardial infarction on the WHO (Rose) questionnaire or who recalled a doctor diagnosis of myocardial infarction or angina, irrespective of electrocardiographic findings (symptomatic). The two groups are mutually exclusive. Because the numbers were small the moderately vigorous and vigorous activity groups (13–20 and 21 +) were combined (fig 6).

SYMPTOMATIC ISCHAEMIC HEART DISEASE

In each physical activity category the rate of heart attack was higher in the men with symptoms than in those without. Both light and moderate physical activity were associated with a lower heart attack rate than in inactive men but this difference was not statistically significant (p = 0·1). At higher levels of physical activity, risk increased but again this difference was not statistically significant (p = 0·1). Case fatality showed no particular pattern. The higher rates in the inactive and occasional activity group may partly reflect the severity of underlying ischaemic heart disease which determines the amount of physical activity possible. The prevalence of recall of a doctor diagnosis of ischaemic heart disease and of definite angina on WHO questionnaire were both higher in the inactive and occasionally active men combined than in the other three groups (p = 0·01). Electrocardiographic evidence of definite myocardial infarction did not differ systematically between the activity groups but definite myocardial ischaemia was least common in the light and moderately active men (6–8 and 9–12). Breathlessness was considerably increased in the inactive men with 44% reporting moderate or severe breathlessness compared with only 12% in the more vigorously active group (≥ 13).

ASYMPTOMATIC ISCHAEMIC HEART DISEASE

There was an increase in the rate of heart attack with increasing physical activity up to the moderate activity level. Although the rate



% Case fatality

IHD (ECG)	43	42	50	36	26
IHD (Symp)	47	44	31	67	35

Figure 6 Heart attack rate (per 1000/year) according to physical activity index in men with symptomatic ischaemic heart disease, asymptomatic ischaemic heart disease, and in men without evidence of ischaemic heart disease. (+) = 13–20 and ≥ 21 combined Adjusted for age, body mass index, social class, and smoking. Number of heart attacks indicated on figure

Table 3 Mean levels (SE) of risk factors according to physical activity index in men with no evidence of ischaemic heart disease

	Physical activity index					
	0–2	*3–5*	*6–8*	*9–12*	*13–20*	*21+*
No of men	442	1706	1307	934	894	431
Systolic blood pressure (mm Hg):						
Mean	143·8	143·0	142·2	142·1	141·0	142·5
SE	(1·00)	(0·69)	(0·74)	(0·81)	(0·84)	(1·08)
Adjusted for HR	142·7	142·7	142·0	142·1	141·3	143·3
Diastolic blood pressure (mm Hg)						
Mean	82·7	81·2	80·7	80·5	79·7	80·6
SE	(0·65)	(0·43)	(0·47)	(0·51)	(0·53)	(0·68)
Adjusted for HR	82·1	81·0	80·6	80·5	79·9	81·1
Cholesterol (mmol/l):						
Mean	6·36	6·40	6·37	6·27	6·35	6·30
SE	(0·06)	(0·04)	(0·04)	(0·04)	(0·04)	(0·06)
HDL cholesterol (mmol/l):						
Mean	1·15	1·14	1·15	1·15	1·17	1·19
SE	(0·01)	(0·01)	(0·01)	(0·01)	(0·01)	(0·01)

All relations adjusted for age, body mass index, social class, and smoking state.
HDL, high density lipoprotein; HR, heart rate.

seemed to fall in the more vigorously active men (>13) the numbers were small. Case fatality was lowest in the most active men. The prevalence of definite myocardial infarction and of definite myocardial ischaemia did not differ in any systematic way between the physical activity groups. Breathlessness (grades 2 and 3 combined) declined from a prevalence of 20·2% in the inactive to 3·8% in the moderately vigorous and vigorously active men. Because this did not relate to the electrocardiographic evidence of myocardial damage it is likely to reflect their degree of physical fitness.

SOCIAL CLASS AND HEART ATTACK

The relation between physical activity and heart attack in men without evidence of ischaemic heart disease was similar in both social classes. Those who carried out moderate or moderately vigorous activity (13–20) showed a large reduction in the risk of heart attack. Risk increased in those in the vigorous activity group in both social classes (data not presented).

PHYSICAL ACTIVITY AND RISK FACTORS

Several studies have suggested that exercise is positively associated with a more favourable risk factor state. Because those with pre-existing ischaemic heart disease are likely to have a greater frequency of adverse risk factors and because the presence of ischaemic heart disease may lead to changes being made in risk factor state, we examined the relation between physical activity and blood pressure and blood lipids in men with no evidence of ischaemic heart disease after adjusting for age, body mass index, social class, and smoking (table 3). There was a tendency for blood pressure to decrease with increasing activity, the decrease being greater for diastolic than for systolic ($p = 0·04$ and $p < 0·01$ respectively). However, in the most active group blood pressures increased slightly. Because physical activity is strongly and inversely associated with heart rate, which is also correlated with systolic and diastolic blood pressure ($r = 0·2$, $p < 0·0001$ and $r = 0·18$, $p < 0·0001$ respectively), adjustments were made for heart rate. The association between physical activity and systolic blood pressure was no longer significant. The association with diastolic blood pressure was reduced considerably but remained significant ($p = 0·03$). Physical activity showed no association with total cholesterol concentration but there was a tendency for high density lipoprotein cholesterol to rise with increasing physical activity ($p < 0·01$). However, high density lipoprotein cholesterol was raised significantly (by 3%) only in the men who were vigorously active.

To assess whether the beneficial effect of physical activity on risk of heart attack is mediated in part by its influence on risk factors (tables 2 and 3) we examined the relation in men without ischaemic heart disease, adjusting as previously for age, body mass index, social class, and smoking status (see fig 5) and then, in addition, for systolic blood pressure, blood lipids, FEV_1, breathlessness, and heart rate. Heart rate has been shown in some studies to be associated with an increased risk of coronary heart disease independent of other risk factors.[16] The findings are presented in terms of relative risks (table 4). After the additional adjustment there was only a small reduction in risk in those who were occasionally or lightly active compared with inactive men. Men who were moderately active or who undertook moderately vigorous activity still showed a significant reduction in the risk of heart attacks. The vigorously active men had the most favourable risk factor state overall, and yet after

Table 4 Adjusted relative risk (and 95% confidence intervals) of heart attack according to physical activity index in 5714 men without pre-existing ischaemic heart disease

Physical activity index	*Adjusted**	*Adjusted† in addition*
0–2	1·0	1·0
3–5	0·8 (0·5 to 1·2)	0·9 (0·5 to 1·3)
6–8	0·8 (0·5 to 1·2)	0·9 (0·6 to 1·4)
9–12	0·4 (0·2 to 0·8)	0·5 (0·2 to 0·8)
13–20	0·4 (0·2 to 0·8)	0·5 (0·3 to 0·9)
21+	0·8 (0·4 to 1·4)	0·9 (0·5 to 1·8)

* Adjusted for age, body mass index, social class, and smoking status.
† Adjusted in addition for systolic blood pressure, total cholesterol, HDL cholesterol, FEV_1, breathlessness, and heart rate.

Table 5 Type and duration/frequency of physical activity, number of men and cases of heart attack, and heart attack rates (per 1000/year) in men with and without pre-existing ischaemic heart disease

			*Rate/1000/year**	
Physical activity	*No (%) of men*	*No of cases*	*No IHD*	*IHD*
Regular walking:				
None	4676 (61)	301	5·5 (3510)	15·6 (1166)
≤20 min/weekday	860 (11)	53	5·4 (647)	14·8 (213)
21–40	996 (13)	62	5·5 (762)	14·4 (234)
41–60	828 (10)	45	3·6 (602)	14·4 (226)
>1 hour	305 (4)	24	6·0 (221)	20·6 (84)
Regular cycling.				
None	7205 (93)	459	5·4 (5378)	15·5 (1827)
≤30 min	294 (4)	16	4·4 (224)	15·1 (70)
>30	207 (3)	10	4·9 (171)	12·4 (36)
Recreational activity				
Inactive	333 (4)	35	8·0 (194)	17·3 (139)
Fairly inactive	906 (12)	76	6·8 (658)	19·3 (248)
Average	2478 (32)	151	5·3 (1847)	15·1 (631)
Fairly active	2086 (27)	125	5·1 (1593)	15·8 (493)
Very active	1899 (25)	98	5·0 (1474)	12·8 (425)
Sporting exercise.				
None	4722 (61)	354	6·1 (3401)	15·1 (1321)
Occasionally	894 (12)	47	4·1 (672)	15·1 (222)
1–3 times/mnth	400 (5)	12	1·8 (333)	18·0 (67)
4–7	770 (10)	30	4·1 (615)	14·8 (155)
8–11	421 (6)	16	3·5 (335)	13·1 (86)
≥12	517 (4)	16	5·9 (428)	20·4 (89)

*Adjusted for age, body mass index, social class, and smoking state.

adjustment the risk of heart attack was only slightly lower than that seen in men who were inactive.

TYPES OF ACTIVITY AND HEART ATTACK

The physical activity index provides a relative measure of overall physical activity. It was of interest to see whether any specific type of activity was most associated with a beneficial effect. "Recreational" work was the most frequent type of leisure activity (table 5) among this population of middle aged British men. Eighty four per cent of the men reported spending at least four hours gardening/ pleasure walking or do-it-yourself work over the weekend. Thirty six per cent of the men did regular walking on weekdays. Twenty five per cent of the men were engaged in regular physical sporting activities (at least once a month) and only 7% cycled regularly.

The attack rate adjusted for age, social class, smoking, and body mass index by the different types of physical activity is shown in table 4 separately in men with and without ischaemic heart disease. These activities are not mutually exclusive. Regular walking was not significantly associated with the risk of heart attack, though in men without ischaemic heart disease those who walked 41–60 minutes a day to and from work (more than a mile each time at fast pace) showed a decreased risk compared with other men ($p = 0·06$). In men with ischaemic heart disease regular walking seemed to have little effect on heart attack rate. The increased rate in those with the longest duration of walking was not significantly different from the rest. In men without ischaemic heart disease cycling was associatied with a small (non-significant) reduction in risk. The number of men with ischaemic heart disease who cycled was too small to draw any inference. Recreational activity was associated with a reduced rate of heart attack in both men with and without ischaemic heart disease. The risk decreased progressively from those who reported being very inactive to those who reported being at least average. This trend was significant for men without ischaemic heart disease ($p = 0·04$) but did not reach significance in those with evidence of ischaemic heart disease. Sporting exercise was significantly associated with a decreased risk in heart attack in men with no previous ischaemic heart disease. Overall, those who did any regular sporting exercise had lower rates than those who did no sporting exercise but the rate did not decrease progressively with increasing frequency of sporting activity. The lowest rates were seen in those who did sporting exercise less than three times a month. Somewhat surprisingly, those who played very frequent sports shared a similar rate to those who did no sporting activity. In men with ischaemic heart disease very frequent sporting exercise (> 12) was associated with a non-significant increase in risk of heart attack.

Table 6 Relative risk of heart attack in men with and without pre-existing ischaemic heart disease according to physical activity index* excluding *all men engaged in sporting activity at least once a month*

	No IHD		*IHD*	
Physical activity	*No*	*RR (95% CI)*	*No*	*RR (95% CI)*
0–2	442	1·0	244	1·0
3–5	1685	0·8 (0·5 to 1·2)	633	0·8 (0·5 to 1·2)
6–8	1210	0·8 (0·5 to 1·2)	434	0·7 (0·4 to 1·1)
9–12	589	0·4 (0·2 to 0·8)	187	0·8 (0·5 to 1·4)
≥13	93	0·3 (0·2 to 1·3)	24	0·9 (0·3 to 3·3)

*Adjusted for age, body mass index, social class, and smoking state.

RISK OF HEART ATTACK AFTER EXCLUSION OF SPORTING ACTIVITY

Morris and his colleagues have indicated that it is only regular sporting exercise that is associated with reduced rates of heart attack,[2–4] whereas others have shown that frequent light or moderate activity is sufficient to produce a beneficial effect.[5–7] We therefore examined the relation between the physical activity index and risk of ischaemic heart disease after excluding all men who reported doing sporting (vigorous) exercise at least once a month. The inverse relation was still seen in men without ischaemic heart disease and was as strong as that seen when sporting activity was included (table 6). Among men with ischaemic heart disease those who were inactive had slightly higher rates than all other men.

Discussion

It is widely accepted that physical activity is associated with a beneficial effect on ischaemic heart disease, with most studies showing an increased risk in sedentary subjects compared with "active" subjects.[1-8 17] Regular physical activity improves physical fitness, and several researchers have suggested that the effect of physical activity on ischaemic heart disease is determined by its influence on physical fitness. Several recent American studies using objective measures of physical fitness have shown a strong inverse association with the risk of coronary heart disease.[18-22] Some studies have found that the relation between physical activity patterns and risk of coronary disease diminishes after adjustment for measures of physical fitness.[20 21] The type and level of physical activity in subjects classified as "active" vary considerably in the different studies and there is still debate as to what type, duration, and intensity of physical activity are required to achieve levels of fitness likely to produce a beneficial effect. Studies in British male civil servants suggest that it has to be regular, aerobic, and vigorous exercise to achieve a beneficial effect.[2-4] In the United States Paffenbarger and colleagues suggested that frequent lighter activities are sufficient to produce a beneficial effect.[5]

BRITISH REGIONAL HEART STUDY

In the present study physical activity showed a strong inverse association with risk of heart attack. Physical activity was strongly associated with smoking, social class, obesity, and prevalence of pre-existing ischaemic heart disease. Men who were inactive were more likely to be smokers, to be manual workers, and to be obese and had a higher prevalence of pre-existing ischaemic heart disease than men who were more active. The inverse association between smoking and physical activity seen in this study is consistent with several other studies. Because the development of ischaemic heart disease is likely to result in changes to the pattern of physical activity, the relation was examined separately in men with and without evidence of ischaemic heart disease. In men with no ischaemic heart disease the risk of heart attack decreased to levels of moderately vigorous activity. Men who carried out moderate or moderately vigorous activity experienced a 50% reduction in risk compared with inactive men even after adjustment for age, social class, smoking, and body mass index. These are men who tend to be engaged in regular sport at least once a week or who engaged in lighter physical activities regularly throughout the week—for example, walking and weekend activities. Moderate to moderately vigorous levels of activity were not only associated with the reduction of heart attacks but these men were also more likely to survive a heart attack than less active men. However, in men who undertook vigorous levels of activity, the risk of heart attacks increased. These men tend to be engaged in vigorous sport at least three times a week. Though the number of men in this group was small, there is a suggestion that the extremes of vigorous exercise may have adverse effects on the heart, particularly in younger middle-aged men (see addendum).

RISKS OF VIGOROUS EXERCISE

The findings of an increased risk in very vigorous subjects has been reported in several other studies.[4 17 22] Paffenbarger *et al* observed an increase in mortality in the top level of energy expenditure—that is, over 3500 kcal/week.[5] The Puerto Rican Heart Study found an increased risk in the most active group.[17] In a study of apparently healthy, middle aged men, Erikssen found an increased risk in the most fit men.[23] In the Multiple Risk Factor Intervention Trial study, although their highest activity category was very broad, they indicated that more vigorous activity did not confer any further protection than did moderately intense activities.[7] Siscovick *et al* found that the risk of primary cardiac arrest is transiently increased during vigorous exercise—that is, risk during exercise among men at the highest level of habitual activity.[24] There is also growing evidence that strenuous exercise may precipitate sudden death in middle aged men.[25] The increased risk seen in our study was only evident in the younger men and may reflect the type of sport undertaken (see addendum).

RISK FACTORS AND PHYSICAL ACTIVITY

Physical activity has been shown to be associated with a favourable influence on risk factors including the reduction of blood pressure and obesity and an increase in high density lipoprotein cholesterol.[26] In the present study physical activity was associated with a small increase in high density lipoprotein cholesterol that was apparent only at the highest levels of activity. This is consistent with several studies that indicate that only strenuous and aerobic exercise increases high density lipoprotein cholesterol.[26] There was a small reduction in blood pressure with increasing physical activity, which was stronger for diastolic than for systolic and largely attributable to the reduction in heart rate associated with physical activity. No association was seen between physical activity and serum total cholesterol. The effects of physical activity on these risk factors are small and are unlikely to explain the relation seen. Physical activity was strongly associated with FEV_1, which has been shown to be a strong predictor of ischaemic heart disease.[15] However, even after adjusting in addition for high density lipoprotein cholesterol, systolic blood pressure, total cholesterol, and FEV_1 the inverse relation persisted. This is consistent with most other studies showing that the risk of ischaemic heart disease associated with inactivity is attenuated but does not disappear after adjusting for coronary risk factors.[5-7 17] Men who were vigorously active had the most favourable risk factors but their risk was similar to inactive men after adjustment.

PRE-EXISTING ISCHAEMIC HEART DISEASE

Most prospective studies examining the relation between physical activity and ischaemic heart disease have excluded men with evidence of cardiovascular disease. Little therefore is known about the long term effects of physical activity in the presence of ischaemic heart disease. Evidence on the effect of exercise comes from clinical trials, which overall have been inconclusive.[27] A recent study on physical training in 11 patients with chronic heart failure suggests that exercise training can increase exercise duration and improve symptoms, but such studies provide no information on ultimate outcome.[28] The inverse pattern clearly seen in men without ischaemic heart disease was not as apparent in men with ischaemic heart disease, though inactive men had the highest risk (fig 5). In men with symptomatic evidence of ischaemic heart disease—that is, those who were aware of their cardiac problem (fig 6)—there was a U-shaped relation, with risk decreasing to levels of light and moderate activity and increasing at more vigorous levels of activity. The implications of this analysis are that light or moderate physical activity in men with symptomatic ischaemic heart disease may be of benefit and that moderately vigorous or vigorous activity may be detrimental. In men with asymptomatic ischaemic heart disease (fig 6) risk tended to increase with increasing activity though the fatality rate decreased. The implication is that although these men achieved increasing cardiopulmonary fitness from increasing physical activity, their risk of heart attack was increased by increasing physical activity.

IS VIGOROUS SPORT ESSENTIAL?

The most popular physical activity was recreational activity—for example, gardening, do-it-yourself, and pleasure walking. Twenty five percent of the men were engaged in regular (at least once a month) vigorous sporting activity. Results from other British studies have suggested that such aerobic exercise is essential to produce a beneficial effect.[4] However, when all men who undertook vigorous sport were *excluded* from the analyses, there was still a strong inverse association, with risk significantly lowered in those who carried out frequent physical activities. Our results accord with those of Paffenbarger *et al* who suggested that regular frequent activity is associated with a reduced rate of heart attack. Several other American studies have shown moderate levels of activity to be sufficient to produce a beneficial effect[5-7] and have shown that benefit is derived from non-vigorous leisure activities such as pleasure walking and gardening. In the British Regional Heart Study recreational activity showed the most consistent relation, with heart attack rates decreasing with frequency of these activities and this was apparent both for men with and without ischaemic heart disease. Vigorous sport was beneficial in men without ischaemic heart disease but there was no dose-response relation with increasing frequency and the risk in those engaged in vigorous sport three or more times a week was similar to those who reported no vigorous activity.

IMPLICATIONS AND RECOMMENDATIONS

Men free of ischaemic heart disease

In this population of middle-aged men, moderate or moderately vigorous physical activity was associated with a significantly decreased risk of heart attack. Moderate physical activity involves frequent recreational activities plus regular walking or vigorous activity once a week. Moderately vigorous activity involves frequent recreational activities, plus cycling or sporting activity at least once a week. However, even if no regular sporting activity is carried out, increasing levels of other forms of physical activity are strongly associated with decreasing risk of heart attack. There seems to be an increased risk of heart attack in younger middle-aged men (40–49) who carry out frequent sporting activity—for example, more than three times a week. While not wishing to sound unduly cautious in an era of jogging, squash, and marathon running, it might be reasonable for men in middle-age considering a programme of vigorous activity to undergo a review of their cardiovascular state. In view of the high prevalence rate of ischaemic heart disease in middle aged British men[29] this is neither alarmist nor unreasonable (see addendum).

Men with ischaemic heart disease

In men with symptomatic ischaemic heart disease physical activity at light or moderate levels is associated with a slightly diminished risk of heart attack. At higher levels of physical activity, however, the rate of heart attack increases and is similar to those seen in inactive men. The message to such men is that light or moderate physical activity is likely to be of benefit. However, undertaking vigorous activity may produce ill effects and they would do well to discuss any proposed activity at a higher level with their physician. In men with asymptomatic ischaemic heart disease detected only by routine electrocardiogram—for example, in health checks, screening programmes, or insurance examinations, although the overall rate of heart attack is lower than in men with symptomatic ischaemic heart disease, the risk of heart attack appears to increase with increasing physical activity. The message must be one of reasonable caution.

Our findings accord with the recent report on medical aspects of exercise from the Royal College of Physician of London which emphasises that "the potential benefits must be weighed against the possible provocation of serious cardiac arrhythmias by those who already have coronary artery disease whether or not it has been recognised."[30] Our findings also suggest that the protective effect is not limited to those taking vigorous aerobic exercise twice weekly and we would encourage a more positive attitude to participation in regular moderate activity in all age groups.

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1 Berlin JA, Colditz A. A meta-analysis of physical activity in the prevention of coronary heart disease *Am J Epidemiol* 1990,132 612–27.
2 Morris JN, Chave S, Adam C, Sirey C Vigorous exercise in leisure-time and the incidence of coronary heart-disease. *Lancet* 1973,i.333–9.
3 Morris JN, Everitt MG, Pollard R, Chave SPW, Semmence AM. Vigorous exercise in leisure-time protection against coronary heart disease. *Lancet* 1980,ii.1207–10.
4 Morris JN, Clayton DG, Everitt MG, Semmence AM, Burgess EH Exercise in leisure time· coronary attack and death rates *Br Heart J* 1990,63:325–34.
5 Paffenbarger RS, Hyde RT, Wing AL, Hsieh CC Physical activity, all cause mortality, and longevity of college alumni *N Engl J Med* 1986;314.605–13
6 Slattery ML, Jacobs DR, Nichaman MZ. Leisure time physical activity and coronary heart disease death· the US Railroad Study. *Circulation* 1989;79:304–11.
7 Leon AS, Connett J, Jacobs DR, Rauramaa R. Leisure time physical activity levels and risk of coronary heart disease and death MRFIT. *JAMA* 1987;258:2388–95.
8 Salonen JT, Slater JS, Tuomilehto J, Rauramaa R. Leisure time and occupational physical activity risk of death from ischaemic heart disease. *Am J Epidemiol* 1988;127 87–94.
9 Shaper AG, Pocock SJ, Walker M, Cohen NM, Wale CJ, Thomson AG British Regional Heart Study. cardiovascular risk factors in middle-aged men in 24 towns *BMJ* 1981,283·179–86.
10 Thelle DS, Shaper AG, Whitehead TP, Bullock DG, Ashby D, Patel I Blood lipids in middle-aged British men. *Br Heart J* 1983;49:205–13.
11 Cook DG, Shaper AG, Macfarlane PW. Using the WHO (Rose) angina questionnaire in cardiovascular epidemiological studies. *Int J Epidemiol* 1989;18 607–13
12 Wilson PWF, Paffenbarger RS, Morris JN, Havlik RJ. Assessment methods for physical activity and physical fitness in population studies: report of a NHLBI workshop. *Am Heart J* 1986,111:1177–92
13 Taylor HL, Jacobs DR, Schucker B, Knudsen J, Leon AS, Debacker G, *et al* A questionnaire for the assessment of leisure time physical activities. *J Chronic Dis* 1978;31 741–55.
14 Blair SN, Kannel WB, Kohl HW, Goodyear N, Wilson PWF Surrogate measures of physical activity and physical fitness. Evidence for sedentary traits of resting tachycardia, obesity and low vital capacity *Am J Epidemiol* 1989,129.1145–6.
15 Cook DG, Shaper AG. Breathlessness, lung function and the risk of heart attack. *Eur Heart J* 1988,9:1215–22.
16 Kannel WB, Kannel C, Paffenbarger RS, Cupples LA. Heart rate and cardiovascular mortality. The Framingham Study. *Am Heart J* 1987;113:1489–94
17 Garcia Palmieri MR, Costas R, Cruz-Vidal M, Sorlie P, Havlik RJ. Increased physical activity: a protective factor against heart attacks in Puerto Rico *Am J Cardiol* 1982;50·749–55.
18 Peters RK, Cady LD, Bischoff DP, Bernstein L, Pike MC. Physical fitness and subsequent myocardial infarction in healthy workers. *JAMA* 1983;249 3052–6.
19 Ekelund LG, Haskell WL, Johnson JL, Whaley FS, Criqui MH, Sheps DS. Physical fitness as a predictor of cardiovascular mortality in asymptomatic North American men. Lipid Research Clinics Mortality Follow-up Study. *N Engl J Med* 1988;319 1379–84.
20 Slattery ML, Jacobs DR. Physical fitness and cardiovascular disease mortality: the US Railroad Study. *Am J Epidemiol* 1988,127:571–80.
21 Sobolski J, Kornitzer M, de Backer G, Dramaix M, Abramowicz M, Degre S, *et al.* Protection against ischaemic heart disease in the Belgian physical fitness study: physical fitness rather than physical activity *Am J Epidemiol* 1988;125:601–10.
22 Blair SN, Kohl H III, Paffenbarger RS, Clark DG, Cooper K, Gibbons LW. Physical fitness and all-cause mortality. *JAMA* 1989,262:2395–401.
23 Erikssen J. Physical fitness and coronary heart disease morbidity and mortality. a prospective study in apparently healthy, middle-aged men. *Acta Med Scand* 1986;(suppl 711):189–92.
24 Siscovick DS, Weiss NS, Fletcher RH, Lasky T. The incidence of primary cardiac arrest during vigorous exercise *N Engl J Med* 1984;811:874–7.
25 Oberman A. Exercise and the primary prevention of cardiovascular disease *Am J Cardiol* 1985;55:10D–20D.
26 Folsom AR, Caspersen CJ, Taylor HL, Jacobs DR, Luepker RV, Gomez-Marin O. Leisure time physical activity and its relationship to coronary risk factors in a population-based sample. the Minnesota Heart Survey. *Am J Epidemiol* 1985;121.570–9.
27 Naughton J. Role of physical activity as a secondary intervention for healed myocardial infarction. *Am J Cardiol* 1985,55:21D–6D.
28 Coats AJ, Adamopoulos S, Meyer T, Conway J, Sleight P. Effects of physical training in chronic heart failure. *Lancet* 1990;335:63–6.
29 Shaper AG, Cook DG, Walker M, Macfarlane PW. Prevalence of ischaemic heart disease in middle aged British men. *Br Heart J* 1984;51:595–605.
30 Royal College of Physicians of London *Medical aspects of exercise; benefits and risks*. 1991.

Addendum

Further analyses strongly suggest that the increased risk of heart attack in men without ischaemic heart disease involved in vigorous levels of physical activity may reflect the presence of hypertension in addition to the type and degree of sporting exertion. This possibility is now being fully examined.

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BRITISH CARDIAC SOCIETY

Staffing in cardiology in the United Kingdom 1990

Sixth biennial survey: with data on facilities in cardiology in England and Wales 1989

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Abstract
The Sixth Biennial Survey of Staffing in Cardiology was conducted in July 1990. This report summarises the data that were collected, together with the results of a survey of facilities in cardiology made in 1989. The total number of cardiologists in the United Kingdom, defined as individuals trained in the specialty and spending at least 40% of their time working in it, is now 323. Six individuals work part time only, making 320 whole time posts. This number has increased over the two years from 1988 to 1990 by 32, of which 23 work only in the specialty and nine as general physicians with a major interest in cardiology. The rate of increase in numbers over the past decade has been reasonably consistent with an average of approximately 4·4% per year. Thirty one districts in England and Wales still have no cardiologist and 13 other districts have little provision with an average of three (visiting) sessions each per week. The population in these 44 districts is 8·3 million. Scotland also has an inadequate distribution of service in the specialty. If recommendations for cardiac surgery and angioplasty made in the Fourth Report of a Joint Cardiology Committee of the Royal College of Physicians of London and the Royal College of Surgeons of England are to be met, we calculate that we need 63 more cardiologists in our major centres. To provide one cardiologist in every district hospital and two for larger districts would require 94 more specialists, making a total shortfall of 157 individuals.

We have no excess of senior registrars to provide for a major expansion at consultant level. Time spent within the senior registrar (or academic equivalent) grade has tended steadily to decline and very few now reach the end of their contracts. The need for more individuals to pass through the senior registrar grade will be met in part by a planned reduction in the training period to three years. This will be inadequate, however, because projected retirements show that the number of consultant vacancies will increase sharply from 1997. We believe that additional senior registrar posts must be created if a serious shortfall in service provision by consultants is to be avoided. The provision of non-invasive facilities in cardiology is reasonable. The need for additional equipment for invasive cardiology has not been assessed. The number of physiological measurement technicians varies considerably between regions and is generally inadequate.

Biennial surveys of staffing in cardiology were first monitored in 1978 and four have been published since 1981.[1-4] We now report the results of the sixth survey of staffing that was conducted in 1990 and the third survey of facilities that were monitored in 1989.

The surveys are conducted under the aegis of the British Cardiac Society and the Cardiology Committee of the Royal College of Physicians. It has a dual purpose: the identification of deficiencies in the provision of cardiological services and the matching of the number of trainee cardiologists with expected consultant vacancies.

The original stimulus for the survey was the excessive number of time expired senior registrars in the specialty in the late 1970s. The information and the predictions for cardiology that have been collected for more than a decade led to an acceptance within the specialty of a reduction in the number of senior registrar posts. A reasonable balance was achieved several years ago between the number of senior registrars completing their training and the number of vacancies at consultant grade. The objectives of the Joint Planning Advisory Committee (JPAC) were therefore anticipated and met even before the committee was set up. So far, no corrective adjustments have been requested in adult cardiology by the JPAC, but the number of senior registrar posts in paediatric cardiology has been increased slightly. The balance may now have tipped in the other direction from that of the 1970s, in that we may have too few

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senior registrar posts. In the recent past only a minority of senior registrars finished their training before entering the consultant grade, and indeed many appointments could be regarded as somewhat premature. This tendency, however, will probably correct itself over the next two or three years because we have relatively few retirements due in the immediate future. Thereafter the position becomes more complex. Important changes are expected from 1997 when the number of consultant vancancies will increase sharply, but the planned three year senior appointments[5] will increase the throughput. We need closer monitoring over these years when numbers will fluctuate. For the foreseeable future, and over the period of these important changes, we intend to undertake surveys of staffing each year instead of biennially, starting from 1991.

Methods of survey

The index date for consultant staffing was July 1990 and that for senior registrars was three months earlier. Most of the data on facilities were collected in 1989 but a few that were missing were obtained retrospectively in 1990.

We approached a contact in every health district in England and Wales and requested cooperation in the completion of the forms used to collect data for the survey. The contacts are cardiologists or general physicians who have an interest in the specialty. Selection is made with the advice of colleagues in the regional cardiac centres to ensure that the contacts are still in post and in a position to offer the help that we require. When the data have been collected they are analysed on a regional basis and sent to at least one cardiologist within that region to check for any obvious errors. We also compare the information with that obtained in previous surveys and check any apparent inconsistencies. The process of data collection and verification is therefore stringent and offers considerable protection against errors important enough to influence predictions. The data on personal projected retirement dates are regarded as confidential and only group data are seen outside the survey offices.

The data from Scotland and Northern Ireland are collected within these countries and subsequently sent to the coordinating centre in Sussex. In Scotland the situation is complex, because many posts are designated as serving general medicine although the incumbents are trained in and practice cardiology. This difficulty necessitated a correction to the 1988 survey for Scotland.[6] The comparative data presented for Scotland in this paper have been collected after detailed enquiries and are believed to be accurate.

The questionnaire on staffing by consultant grades has two sections. One is for those who practise in the specialty virtually all of their professional time. The other, which tends to relate to district hospitals, is for physicians with a major interest in the specialty; to qualify for inclusion they should have had an appropriate training in cardiology and should retain a major interest with at least 40% of their professional time spent in the specialty. Accreditation is not yet used as a criterion because most practitioners were appointed before this was available.

The questions in the facilities survey relating to invasive and non-invasive facilities were reasonably straightforward. The term "major haemodynamic facilities" refers to left heart studies (pressure measurements and angiography) whereas "minor haemodynamic studies" refers to right heart measurements such as bedside pressure monitoring with Swan-Ganz catheters. A cardiac care unit is defined as an area of monitored beds with a central console and fluoroscopy immediately available within the same area. Stress testing could be either with a treadmill or a bicycle ergometer.

The format of the tables is similar to that used in previous publications. Most tables show comparable data from the 1988 survey,[4] presented within brackets.

Comments

STAFFING: CONSULTANT GRADE

Table 1 shows the overall numbers of consultant cardiologists in England and Wales from 1980 to 1990. Figure 1 shows the increase over the decade. As in the relevant tables, the bar charts indicate separately those engaged only in cardiology and those who are general physicians with both special training and a major interest in cardiology. A division is made also into adult and paediatric posts, giving four subdivisions in all. (The number of physicians designated as having only a major interest in paediatric cardiology is small or absent, so that only three components are seen in most of the bars in fig 1). The overall increase in numbers over the decade has been 98 posts (44%) with

Table 1 Cardiovascular physicians in England and Wales, 1980–1990

	Cardiology only		*Major interest*		
Year	*Adult*	*Paediatric*	*Adult*	*Paediatric*	*Totals*
1980	103	19	98	3	223
1982	111 (8%)	18 (– 5%)	117 (19%)	4 (33%)	250 (12%)
1984	111 (8%)	29 (53%)	121 (23%)	6 (100%)	267 (20%)
1986	119 (16%)	31 (63%)	118 (20%)	2 (– 33%)	270 (21%)
1988	130 (26%)	33 (74%)	128 (31%)	0 (0%)	291 (30%)
1990	145 (42%)	39 (105%)	134 (37%)	2 (– 33%)	320 (43%)

The 1990 figures show the number of whole time equivalents (WTEs) There are six half posts, so the total of individuals is 323. The accompanying graph also shows WTEs for 1990. Percentage increases since 1980 are shown in brackets.

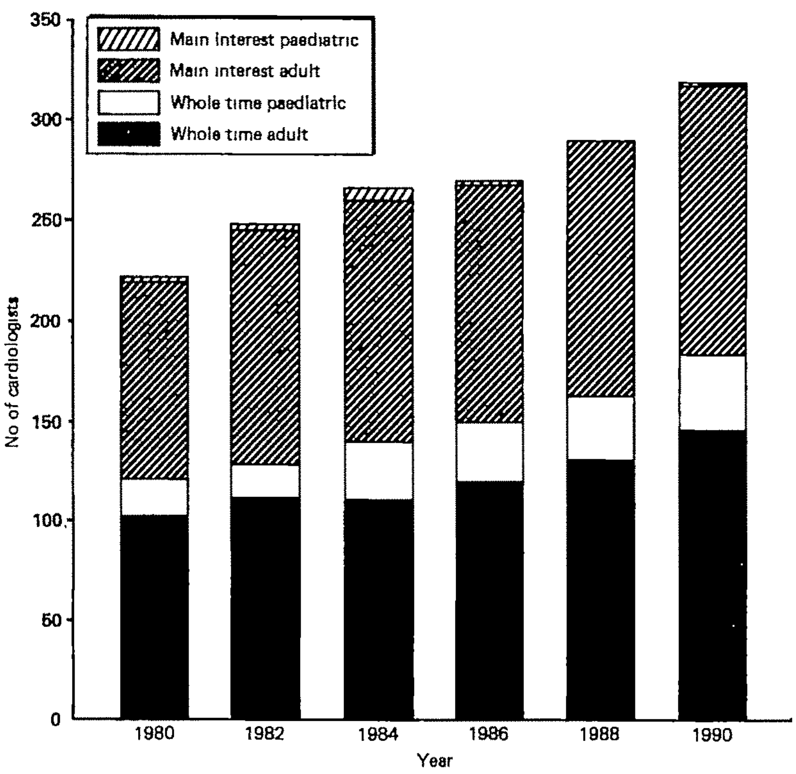

Figure 1 Increase over a decade in the number of consultant posts in cardiology in the United Kingdom

changes for cardiology only (adult), cardiology (paediatric), and major interest (adult), being respectively 44 posts (42·7%), 20 posts (95%), and 35 posts (35%). The average yearly increases are, of course, approximately one tenth of these figures.

Table 2 shows data for England and Wales listed by region with latest population figures, number of health districts, number of major cardiac centres undertaking surgery, and the numbers of cardiologists (both totals and the subdivisions as in table 1). The health districts in Wales are organised somewhat differently from those in England with a usual pattern of two district general hospitals in each (one health district has none). The number has not changed but we have presented the Welsh data differently in the current survey, with data based on districts as for England rather than on district general hospitals as we did previously. There are two fewer health districts in England as a result of reorganisation. The number of cardiologists has increased by 32 over the two year period 1988 to 1990. Twenty three of these new posts are in full time adult cardiology. The smaller apparent increase of 29 shown in the table represents greater precision in the reporting of data: previously six part-time posts were each scored as a whole unit whereas they are now scored as half a unit.

Tables 3 and 4 show comparable data for Scotland and Northern Ireland. Some inconsistency in the reporting of posts with an interest in cardiology (reflecting different traditions for designation compared with that in England) have led to a further retrospective change in the 1988 data after our published correction.[6] The increase of three in the number of posts reported now is, however, real and not an artefact of reclassification. Scotland has one cardiologist per 121 000 population compared with one per 63 000 population in Northern Ireland and one per 157 000 in England and Wales.

Tables 5–7 show expected retirements of cardiologists in the United Kingdom from 1990 to 2005, and the same information for England and Wales appears as a bar chart in fig 2. The purpose of the figure is to illustrate the tendency to a stepped increase in expected vacancies from 1997 onwards. This has important planning implications for the number of training posts, but the JPAC formula (intended to achieve a balance between training posts and consultant vacancies) makes no allowances for such predictions. Planning depends on a formula based on historical vacancies with an additional allowance for growth that is also based on historical data. We recognise that the Department of Health does not have access to reliable forward predictions, but we hope that

Table 2 Cardiovascular Physicians (WTEs) by region in England and Wales at 1 July 1990 (Office of Population Censuses and Surveys, figures in thousands) (1988 data in parentheses)

				Cardiology only		*Major interest*		
Region	*Population mid–1988*	*No of HDs*	*No of MCs*	*Adult*	*Paediatric*	*Adult*	*Paediatric*	*Totals*
East Anglia	2 034 4	8 (8)	1	4 0 (3)		5 5 (6)		9 5 (9)
Mersey	2 403 9	10 (10)	1	4 0 (4)	3 0 (3)	6 0 (5)		13 0 (12)
North East Thames	3 776 4	16 (16)	3	15·5 (12)		9 0 (10)		24 5 (22)
North West Thames*	3 470 4	13 (15)	3	11 0 (16)	1 0 (2)	7 0 (7)		19 0 (25)
North Western	3 989 6	19 (19)	3	9 0 (9)	3 0 (2)	12 0 (12)		24 0 (23)
Northern	3 071 0	16 (16)	1	8 5 (6)	3 0 (2)	9 0 (11)		20 5 (19)
Oxford	2 523 7	8 (8)	1	4 0 (4)	2 0 (2)	7 0 (7)		13 0 (13)
South East Thames	3 651 6	15 (15)	4	15 0 (15)	4 0 (4)	9 0 (8)		28 0 (27)
South West Thames	2 961 4	13 (13)	1	9 0 (7)		6 0 (8)	1 0	16 0 (15)
South Western	3 236 0	11 (11)	1	6 0 (5)	3 0 (2)	5 0 (6)		14 0 (13)
Trent	4 662 4	12 (12)	3	8 0 (6)	1 0 (1)	12·5 (11)	1 0	22 5 (18)
Wessex	2 928 4	10 (10)	1	3 0 (2)	3 0 (2)	11 0 (8)		17 0 (12)
West Midlands	5 205·3	22 (22)	3	14 0 (13)	3 0 (3)	15 0 (11)		32 0 (27)
Yorkshire	3 620 1	17 (17)	3	12 0 (10)	3 0 (3)	11 0 (9)		26 0 (22)
Wales†	2 857 0	9 (9)	1	4 0 (4)		9 0 (9)		13 0 (13)
Special hospitals		4 (4)	4	18 0 (14)	10 0 (7)			28 0 (21)
Totals	50 393 3	203 (205)	34	145 0 (130)	39 0 (33)	134 0 (128)	2 0 (0)	320 0 (291)

*Owing to reorganisation (Hammersmith and Brent) North West Thames has two HDs less than in 1988.
†Wales has 18 (18) district hospitals.
HD, health district; MC, major centre
Notes· (*a*) South West Thames and Wales show minor updates to published 1988 data
(*b*) Regions with half posts: Northern (1, will not be replaced), Trent (1), East Anglia (1), North East Thames (1), South East Thames (2)
(*c*) The 1988 data show the number of physicians not the number of WTEs
(*d*) Blanks in the tables represent either zero values or data not appropriate. This is for ease of reading and does not imply missing values

Table 3 Cardiovascular physicians by health board in Scotland at 1 July 1990 (Office of Populaton Censuses and Surveys, figures in thousands)

Health district	*Population mid-1989*	*Cardiology only*		*Major interest*		*Totals*
		Adult	*Paediatric*	*Adult*	*Paediatric*	
Argyll and Clyde	441 2			2 (1)		2 (1)
Ayrshire and Arran	374 5			2 (2)		2 (2)
Borders	102 7					
Dumfries and Galloway	147 6			1 (1)		1 (1)
Fife	344 8					
Forth Valley	271 4					
Grampian	503 5	3 (3)				3 (3)
Greater Glasgow	933 2	9 (9)	3 (3)	6 (5)		18 (17)
Highland	201 9			1 (1)		1 (1)
Lanarkshire	562 3			3 (3)		3 (3)
Lothian	742 9	7 (6)	2 (2)	1 (1)		10 (9)
Orkney	19 4					
Shetlands	22 2					
Tayside	392 5	2 (2)				2 (2)
Western Isles	30 6					
Totals	5 090 7	21 (20)	5 (5)	16 (14)		42 (39)

Notes (*a*) Dumfries and Glasgow show minor updates to previously published data
(*b*) One new whole time adult post in Edinburgh not established
1988 data are shown in parentheses.

Table 4 Cardiovascular physicians by health board in Northern Ireland at 1 July 1990 (Office of Populaton Censuses and Surveys, figures in thousands)

Health district	*Population mid-1989*	*Cardiology only*		*Major interest*		*Totals*
		Adult	*Paediatric*	*Adult*	*Paediatric*	
Eastern HSSB	645·9	11 (10)	2 (2)	2 (3)		15 (15)
Northern HSSB	385·7			4 (3)		4 (3)
Southern HSSB	291·2			3 (3)		3 (3)
Western HSSB	260 2			3 (3)		3 (3)
Totals	1 583 0	11 (10)	2 (2)	12 (12)		25 (24)

1988 data are shown in parentheses.
HSSB, Health and Social Services Board.

an appropriate response will be made for the data that we have collected. The numbers in brackets in tables 5–7 show the predictions for retirements that were made in 1988 for the same years. The pattern is very similar, but inevitably there are minor differences year to year reflecting inconsistencies in the dates of intended early retirement. These small differences do not change our overall predictions, and the similarity of the pattern is reassuring.

The data in tables 8–10 continue to disappoint. Although the number of cardiologists has increased overall, we still have many districts with no representative of the specialty and others in which provision is clearly inadequate. If the present tables are compared with those in our previous report, apparent inconsistencies will be noticed: this is a consequence of more refined data and does not represent inaccuracies. We have now included in tables 8–10 not only lack of provision but also inadequate provision (defined as less than seven sessions per week, usually provided by visiting specialists). Thus in England and Wales we now have 31 districts with no cardiologist (total population 5·46 million) compared with 45 in 1988 and 54 in 1986. But an additional 13 districts (total population 2·84 million) have inadequate provision with an average of only three sessions each. In Scotland six health

Table 5 Cardiovascular physicians expected to retire each year in England and Wales (as of 1 July 1990)

Year	*Cardiology only*			*Major interest*			*Grand total*
	Adult	*Paediatric*	*Total*	*Adult*	*Paediatric*	*Total*	
Not stated*	3		3	1		1	4
1990	1		1	1		1	2 (3)
1991	3		3	1		1	4 (5)
1992	1		1	1		1	2 (4)
1993	3	1	4	1		1	5 (9)
1994	3		3	1		1	4 (4)
1995	4		4	1	1	2	6 (5)
1996	3		3	2		2	5 (6)
1997	5		5	8		8	13 (10)
1998	3		3	2		2	5 (6)
1999	1	2	3	8		8	11 (13)
2000	5	2	7	7		7	14
2001	4	1	5	2		2	7
2002	3		3	9		9	12
2003	2	2	4	2		2	6
2004	6	2	8	4		4	12
2005	6	2	8	3		3	11
2006 or later	91	27	118	81	1	82	200
Totals	147	39	186	135	2	137	323

*Mainly locum posts
The grand total expected to retire each year, as given in 1988, is shown in parentheses.

Table 6 Cardiovascular physicians expected to retire each year in Scotland (as of 1 July 1990)

Year	Cardiology only			Major interest			Grand total
	Adult	*Paediatric*	*Total*	*Adult*	*Paediatric*	*Total*	
1990		1	1				1 (1)
1991	1		1				1 (1)
1993				1		1	1 (1)
1995	1		1	2		2	3
1997	1		1				1
2000	1		1	1		1	2
2003	1		1	1		1	2
2004				2		2	2
2005	1	1	2	1		1	3
2006 or later	15	3	18	8		8	26
Totals	21	5	26	16		16	42

1988 data are shown in parentheses.

Table 7 Cardiovascular physicians expected to retire each year in Northern Ireland (as of 1 July 1990)

Year	Cardiology only			Major interest			Grand total
	Adult	*Paediatric*	*Total*	*Adult*	*Paediatric*	*Total*	
1992	1		1				1 (1)
1997	1		1				1 (1)
1998	1		1				1 (1)
2001				1		1	1
2004	2	1	3	1		1	4
2005	2		2				2
2006 or later	4	1	5	10		10	15
Totals	11	2	13	12		12	25

1998 data are shown in parentheses.

boards have no cardiologists. The situation in Northern Ireland is probably satisfactory because of the close cover provided for the small two district hospitals without their own specialists.

Our data for consultant numbers do not agree with those published by the Department of Health, based on Korner statistics.[7] The department has a subdivision between "main specialty" and "second specialty", presumably reflecting our own division between "whole time" and "major interest" physicians. There is no separate designation for paediatric cardiology. The department's figures (1989) for "main specialty" totalling 148 individuals contrast with ours (1990) of 184 for adult plus paediatric cardiology. For "second specialty" the discrepancy is greater: 79 against 136. Thus the total shortfall against our carefully collected figures is 93, with only 10 months difference between the index dates for data collection. The discrepancy may be due in part to differen-

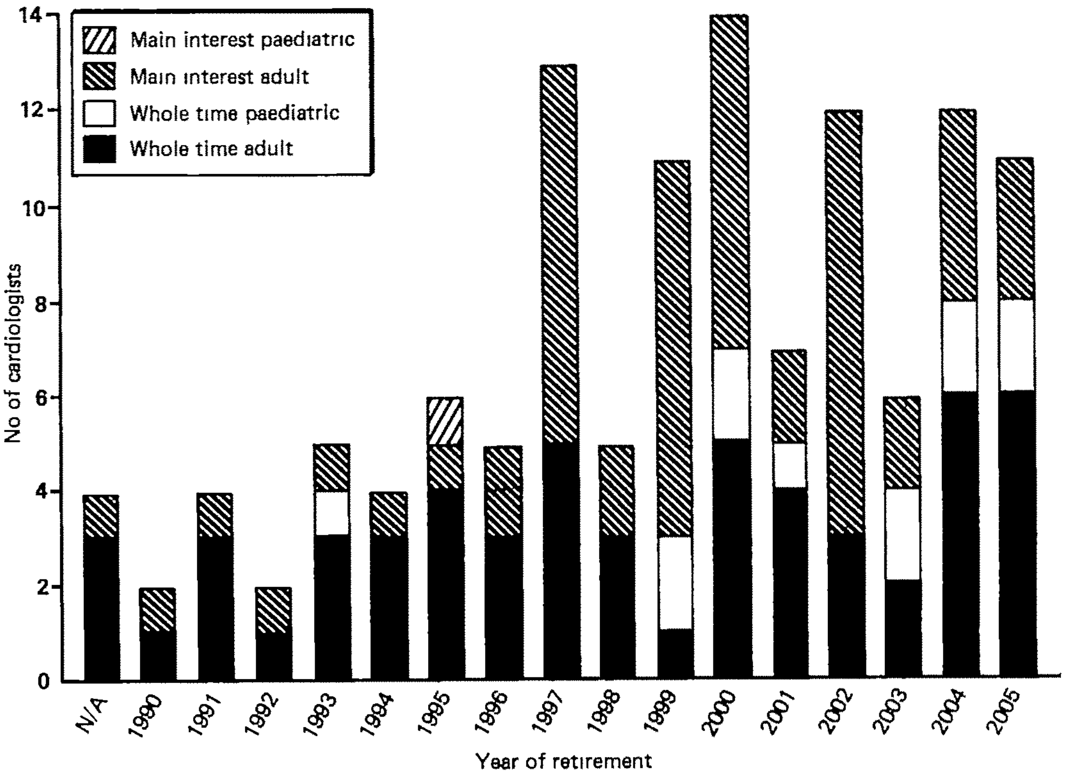

Figure 2 Projected retirements of cardiologists from 1990 to 2005. There is a tendency for a substantial increase from 1997 onwards

Table 8 Health districts without cardiologists by region in England and Wales at 1 July 1990

Region	*Population mid-1988*	*No of Hds*	*No of Hds without*	*Losses*	*Gains*	*HD population without*
East Anglia	2 034 4	8 (8)	2 (3)		1	419·5
Mersey	2 403·9	10 (10)	5 (6)		1	974·1
North East Thames	3 776 4	16 (16)	2 (3)		1	517 6
North West Thames*	3 844 1	13 (15)	3 (4)		1	716·7
North Western	3 989 6	19 (19)	5 (5)			865 6
Northern	3 071 0	16 (16)	6 (6)			994·4
Oxford	2 523 7	8 (8)				
South East Thames	3 651 6	15 (15)	(1)		1	
South West Thames	2 961 4	13 (13)	3 (3)	1	1	727·2
South Western	3 236 0	11 (11)	3 (3)			569 8
Trent	4 662·4	12 (12)	2 (4)		2	525 0
Wessex	2 928 4	10 (10)	2 (3)		1	250 8
West Midlands	5 205 3	22 (22)	6 (8)		2	1 037 1
Yorkshire	3 620 1	17 (17)	3 (3)			479·8
Wales†	2 857 0	9 (9)	2 (1)	1		227 7
Special hospitals		4 (4)				
Totals	50 393 3	203 (205)	44 (53)	2	11	8 305·3

*Owing to reorganisation North West Thames has two HDs less than in 1988 (Hammersmith and Brent).
†Although there is an apparent loss in Wales, the number of DGHs without (eight of 18) has not changed.
This table shows the number of HDs that have fewer than seven cardiology sessions per week.
The 1988 data have been re-calculated to the same definition and are shown in parentheses.
The number of HDs completely without in 1990 was 31 (45 in 1988) and 13 more HDs had on average only three sessions each.
Ten HDs counted as having a cardiologist had fewer than 10 sessions each.

Table 9 Scottish health boards without cardiologists at 1 July 1990 (Office of Population Censuses and Surveys, figures mid-1989 in thousands)

Health Board	*Population without*
Borders	102 700
Fife	344 800
Forth Valley	271 400
Orkney	19 400
Shetlands	22 170
Western Isles	30 630
Total	791 100

No change from (updated) 1988 figure of six health boards without.

ces in designation among those practising cardiology between "second specialty" consultants and general physicians. This cannot account, however, for the major difference between the two surveys in the numbers for specialist cardiologists or paediatric cardiologists without a general medical commitment. The Department of Health is aware of our own statistics and for the purposes of the JPAC has accepted them in the past. Consultant numbers determine the number of training posts, so we hope they will continue to do so. A reconciliation of the department's data with our own, district by district, would be ideal but is apparently impracticable.

STAFFING: SENIOR REGISTARS

Tables 11 and 12 show the numbers within regions of cardiologists, senior registrars, and major cardiac centres. As far as we are aware all the major centres within teaching hospitals have senior registrars. The Brook Hospital in South East Thames was officially designated as a regional cardiac centre though it is not administered by a teaching authority and has no senior registrar. There has been no change overall in the number of senior registrars compared with 1988, though there have been a few changes in distribution. Table 13 shows that only 13 senior registrar contracts are expected to expire in 1991 and 1992, but 35 had been in post less than two years at the time of the 1990 survey (with three posts vacant). Four senior registrars were time expired and employed on extended contracts. In general, far more senior registrars are being appointed before they complete their training period than continue beyond the first expiry date. The number of expected consultant vacancies for the ensuing four years is also appreciably less than the number of senior registrars due to finish training. This is a familiar pattern that has been mentioned in previous surveys, due principally to the growth in consultant numbers of four to five per cent per annum. The apparent mismatch has not prevented the average time in post as senior registrar tending to become progressively shorter. The figures in tables 14 and 15 for Scotland and Northern Ireland are too small to exert any major influence on the position overall for the United Kingdom.

Table 10 Northern Ireland health boards without cardiologists at 1 July 1990 (Office of Population Censuses and Surveys, figures mid-1989 in thousands)

Health Board	*No of UoMs*	*No of UoMs without*	*Health board population*	*UoM Pop without*
Eastern HSSB	6	2 (2)	645 9	115 2
Northern HSSB	4	(1)	385·7	
Southern HSSB	3		291 2	
Western HSSB	3		260 2	
Total	16	2 (3)	1 583 0	115·2 (305 0)

UoM, Unit of management; HSSB, Health and Social Services Board.

STAFFING: PHYSIOLOGICAL MEASUREMENT TECHNICIANS

Technical assistance is crucial to the effective operation of cardiac centres and departments of cardiology in district hospitals—yet we have no official norm for staffing levels. Table 16 shows the wide disparity in the number of qualified and trainee technicians (recorded as whole time equivalents) in each region, both as totals and as numbers per hundred thousand patients. Such data must be interpreted with care, particularly where relative overprovision might be inferred. For example, Mersey has the largest number of technicians pro rata but very few cardiographers. We can deduce that the technicians take the electrocardiograms, a practice which increases flexibility and which, in some situations, may be cost effective.

Table 11 *Cardiovascular physicians and senior registrars by region of England and Wales at 1 July 1990 (1988 data in parentheses)*

Region	*No of HDs*	*Cardiology only*	*Major interest*	*Total cardiologists*	*Senior registrars*	*No of MCs*
East Anglia	8	4	6	10	1 (1)	1
Mersey	10	7	6	13	3 (3)	1
North East Thames	16	16	9	25	4 (4)	3
North West Thames*	13	12	7	19	3 (4)	3
North Western	19	12	12	24	2 (4)	3
Northern	16	12	9	21	3 (3)	1
Oxford	8	6	7	13	2 (3)	1
South East Thames	15	20	9	29	3 (4)	4
South West Thames	13	9	7	16	1 (1)	1
South Western	11	9	5	14	2 (2)	1
Trent	12	9	14	23	3 (4)	3
Wessex	10	6	11	17	1 (2)	1
West Midlands	22	17	15	32	3 (4)	3
Yorkshire	17	15	11	26	4 (5)	3
Wales†	9	4	9	13	3 (3)	1
Special hospitals	4	28		28	8 (9)	4
Totals	203 (205)	186 (163)	137 (128)	323 (291)	46‡ (56)	34

*Owing to reorganisation North West Thames has two districts less than in 1988. † Wales has 18 district hospitals
‡There were four vacant senior registrar posts in adult cardiology.
Numbers refer to cardiologists not whole time equivalents MC, major centre.

Table 12 *Cardiovascular physicians and senior registrars in Scotland and Northern Ireland at 1 July 1990*

Region	*No of HBs*	*Cardiology only*	*Major interest*	*Total cardiologists*	*Senior registrars*	*No of MCs*
Scotland	15	26	16	42	7	2
Northern Ireland	4	13	12	25	2	1

Note: Northern Ireland had three vacant senior registrar posts in adult cardiology.
Mc, major centre; HB, health board.

Moreover, most technicians have duties in other disciplines—for example in respiratory function or in a vascular laboratory. While our respondents have been asked to allow for this confounding variable, it is difficult to do so with any degree of accuracy. We know, however, that the bleak situation shown for Oxford and Wessex does reflect a very unsatisfactory situation which must detract from the efficiency of the two centres within these regions.

In 1987 the British Cardiac Society report on Cardiology in the District Hospital[8] recommended that four technicians dedicated to cardiology were needed for each 250 000 population (in addition to cardiographers). Cardiac centres undertaking catheterisation, angiography, angioplasty, electrophysiology, and other technically demanding procedures need an appreciably higher ratio. Relatively little change has occurred from 1984 to 1989. The increase of 84 in technician numbers must be considered alongside the decrease in cardiographers of 31. The net increase of 53 (4%) can make little impression on the delays and constraints in the performance and reporting of the investigations that are crucial for the optimal management of most patients with heart disease.

STAFFING: MISCELLANEOUS

Sixty districts reported that a resuscitation training officer was employed, but usually this is part time only and often combined with other duties. We know from other sources of 23 full time resuscitation training officers. The Royal College of Physicians recommended in 1987 that every district should employ a resuscitation training officer. Most have not heeded this advice though no other technical post could make as much impact in reducing the number of patients dying from potentially treatable causes. We have no previous data on rehabilitation facilities, but we were told of 113 programmes within the 214 districts of England and Wales. We have no details of these but a report on rehabilitation within the United Kingdom has been prepared and is in the press.[9] Many may offer very limited facilities: we can be certain that nearly half the districts offer none.

FACILITIES

The 1989 survey (conducted one year earlier than the staffing survey reported above) did not include Scotland and Northern Ireland. Table 17 for England and Wales shows few surprises. Some of the minor changes in the number of cardiac care units may be due to differences in the interpretation of our definition. We are aware that a few hospitals with an appreciable acute workload are still without any cardiac care units but, in general, distribution throughout the country is reasonable. We made no enquiry about numbers of beds in relation to population. Cardiac surgery is performed in

Table 13 *Contract expiry dates for senior registrars compared with retirement dates for consultants in England and Wales at 1 July 1990*

Year	*SR contracts expiring*	*Consultants retiring*	*Balance*
1991	4	4	
1992	9	2	7
1993	16	5	11
1994	11	4	7
1995	3	6	−3
Totals	43	26	17

Notes: (*a*) Five SR contract expiry dates are not known.
(*b*) One post was discontinued after survey date, the senior registrar is now consultant, contract date not relevant.

Table 14 Contract expiry dates for senior registrars (SR) compared with retirement dates for consultants in Scotland at 1 July 1990

Year	*SR contracts expiring*	*Consultants retiring*	*Balance*
1991	2	1	1
1992	1		1
1993	2	1	1
1994	1		1
Totals	6	2	4

Note One senior registrar contract expiry date is not known.

Table 15 Contract expiry dates for senior registrars (SR) compared with retirement dates for consultants in Northern Ireland at 1 July 1990

Year	*SR contracts expiring*	*Consultants retiring*	*Balance*
1990			
1991			
1992	1	1	
1993			
1994	1		1
Totals	2	1	1

Note: Three senior registrar contract expiry dates are not known

two fewer centres (both in the North West Thames Region) owing to health district reorganisation but the number of hospitals carrying out cardiac surgery remains unchanged. A few centres without cardiac surgery undertake left heart studies and four of them also offer angioplasty. Only five districts cannot offer temporary pacing and in some of these a provision available nearby offers at least a partial solution. In general, however, we believe that every hospital taking acute emergencies should have immediate provision for temporary pacing and any deficiency in this respect is dangerous and unacceptable.

Table 18 shows that 190 of the 212 districts have echocardiographic facilities—an increase of 50 since the previous survey in 1984. Appreciably more centres can offer cross-sectional echocardiography, which explains the decrease in M mode facilites. Over 100 districts also have Doppler imaging and half of them have colour flow Doppler imaging. Fewer districts report that they are undertaking cardiac scintigraphy (unfortunately it is not possible to make an accurate comparison of the scintigraphy figures from 1984 because those data were incorrectly calculated).

Most districts, however, have facilities for ambulatory monitoring and stress testing. These facilities are now distributed satisfactorily and will not need regular surveys in future years. Greater attention can then be paid to other aspects of the quality of service that can be offered.

We note an important increase in the number of ambulances with defibrillators from 1986 to 1989. This may have less relevance after the decision by the Secretary of State that all frontline ambulances should carry defibrillators.[10] We believe this to be an important initiative.

Consultant staffing: a statement of need

The need for cardiologists both at cardiac centres and district general hospitals has increased substantially over two or three decades for several major reasons. First, the development of coronary artery bypass grafts and percutaneous coronary angioplasty has created a huge workload in the assessment of potential candidates for these procedures. Secondly, the need for angioplasty, balloon dilatation of valves, and therapeutic catheter procedures for patients with congenital heart disease has also led to the development of the concept of the interventionist physician within the specialty. Thirdly, the control of arrhythmias by pacing, by drugs, and by surgery has become complex but highly successful: it calls for specialist skills that cannot readily be provided by a general physician. Fourthly, management of patients with serious heart disease in hospitals outside major cardiac centres is no longer straightforward: therapeutic agents such as modern antiarrhythmics and thrombolytics have potential for considerable harm as well as benefit, while investigations such as echocardiography, stress testing, and ambulatory monitoring demand training and

Table 16 Technical support in cardiology by region in England and Wales at 1 March 1989 (1984 data are given in parentheses)

		Physiological measurement technicians							
						Since 1984			
Region	*No of HDs*	*Qualified*	*Trainee*	*Total*	*Per 100 000*	*Increase*	*Decrease*	*Per 250 000 population*	*Cardiographers*
East Anglia	8 (8)	20 (15)	2 (5)	22 (20)	1·1 (1 0)	0 09		2·04	24 (21)
Mersey	10 (10)	38 (65)	16 (18)	54 (83)	2 2 (3 4)		1 18	4 16	3
North East Thames	16 (16)	62 (53)	4 (14)	66 (67)	1 7 (1 8)		0 05	2 86	45 (30)
North West Thames*	13 (15)	51 (28)	10 (19)	61 (47)	1·7 (1 4)	0 40		2 75	34 (35)
North Western	19 (19)	104 (83)	18 (14)	122 (97)	3·1 (2·4)	0 62		5 08	17 (19)
Northern	16 (16)	26 (33)	11 (6)	37 (39)	1·2 (1·2)		0·03	1 86	35 (37)
Oxford	8 (8)	14 (11)	2 (2)	16 (13)	0 6 (0·5)	0 10		1 08	20 (20)
South East Thames	15 (15)	42 (41)	8 (10)	50 (51)	1·4 (1 4)		0 05	2 36	41 (51)
South West Thames	13 (13)	32 (21)	8 (6)	40 (27)	1 4 (0 9)	0 44		2 35	19 (18)
South Western	11 (11)	38 (32)	7 (2)	45 (34)	1·4 (1·1)	0 34		2 68	31 (29)
Trent	12 (12)	75 (82)	18 (22)	92 (104)	2 0 (2 3)		0 28	3 41	21 (44)
Wessex	10 (10)	21 (16)	4 (5)	25 (21)	0·8 (0 7)	0·11		1 65	25 (28)
West Midlands	22 (22)	89 (81)	8 (7)	97 (88)	1 9 (1 7)	0 17		3·24	36 (35)
Yorkshire	17 (17)	72 (65)	16 (8)	88 (73)	2·4 (2 0)	0 42		4·01	26 (31)
Wales†	9 (9)	84 (65)	16 (19)	100 (84)	3·5 (3 0)	0 52		6 64	18 (34)
Special Hospitals	4 (5)	59 (43)	8 (9)	67 (52)					7 (3)
Totals	203 (206)	827 (731)	155 (166)	981 (897)	1·9 (1 8)	0·15		3 36	402 (433)

*Hammersmith is now shown under special hospitals.
†Wales has 18 (18) district hospitals.
Staff numbers are in rounded WTEs. For population see table 17.

Table 17 Cardiac facilities (number of HDs with given facility) by region in England and Wales at 1 March 1989 (Office of Population Censuses and Surveys' figures in thousands)

					Haemodynamic				*Pacing*	
Region	*Population mid-1988*	*No of HDs*	*No of CCUs*	*Cardiac surgery*	*Major*	*Minor*	*PTCA*	*Invasive EP*	*Permanent*	*No Temp‡*
East Anglia	2 034·4	8 (8)	9 (8)	1 (1)	2 (2)	7 (5)	1 (1)		2 (2)	
Mersey	2 403 9	10 (10)	10 (9)	1 (1)	1 (1)	6 (3)	1 (1)	1 (1)	1 (1)	(1)
North East Thames	3 776 4	16 (16)	19 (15)	3 (3)	4 (4)	10 (9)	4 (3)	3 (3)	4 (4)	
North West Thames*	3 470·4	13 (15)	15 (14)	2 (4)	4 (5)	9 (9)	3 (3)	4 (4)	4 (6)	
North Western	3 989 6	19 (19)	20 (19)	3 (3)	4 (3)	12 (11)	3 (2)	4 (3)	5 (5)	1 (2)
Northern	3 071 0	16 (16)	21 (21)	1 (1)	1 (1)	8 (6)	1 (1)	1 (1)	1 (1)	
Oxford	2 523·7	8 (8)	6 (5)	1 (1)	1 (1)	6 (5)	1 (1)	1 (1)	2 (1)	1 (1)
South East Thames	3 651 6	15 (15)	19 (17)	4 (4)	5 (4)	11 (9)	4 (4)	6 (5)	7 (6)	
South West Thames	2 961 4	13 (13)	12 (11)	1 (1)	2 (2)	12 (7)	1 (1)	2 (2)	3 (2)	
South Western	3 236 0	11 (11)	13 (12)	1 (1)	1 (1)	7 (6)	2 (1)	6 (3)	5 (5)	
Trent	4 662 4	12 (12)	16 (15)	2 (2)	3 (3)	8 (7)	2 (2)	2 (2)	4 (3)	(2)
Wessex	2 928 4	10 (10)	9 (10)	1 (1)	1 (1)	6 (4)	1 (1)		3 (2)	
West Midlands	5 205·3	22 (22)	24 (25)	3 (3)	6 (8)	15 (15)	4 (1)	4 (5)	11 (9)	1 (1)
Yorkshire	3 620 1	17 (17)	17 (13)	3 (3)	4 (3)	11 (8)	3 (2)	5 (2)	6 (5)	1 (3)
Wales†	2 857 0	9 (9)	15 (12)	1 (1)	1 (2)	6 (6)	1 (2)	1 (1)	2 (2)	1 (1)
Special hospitals		4 (5)	4 (2)	4 (4)	4 (4)	3 (5)	3 (4)	4 (4)	4 (4)	
Total	50 393·3	203 (206)	229 (208)	32 (34)	44 (45)	137 (115)	35 (30)	44 (37)	64 (58)	5 (11)

*Hammersmith now shown under special hospitals.
†Wales has 18 district hospitals.
‡HDs without temporary pacing facilities
1984 data are shown in parentheses.

skill. Finally, an optimal service calls for commitment to the prevention of heart disease, to training in resuscitation, and to the provision of rehabilitation programmes. These needs are poorly met at present.

A report of the Royal College of Physicians of London and the Royal College of Surgeons of England recommended that every health district with four or more physicians should have one trained in cardiology.[11] But table 8 shows that 31 districts have no cardiologists and that 13 others have minimal visiting representation, so that overall there is a serious shortfall in 44 districts on this basis. Subsequent to the Royal Colleges' recommendation, the British Cardiac Society stated that each large district (over 250 000) required two cardiologists for the provision of an adequate service.[8] Other major specialties such as gastroenterology and respiratory medicine have made similar recommendations. These estimates have not been contested in discussions relating to manpower either within the college or outside it, and indeed they are crucial to the concept of a consultant based service. According to this criterion a total of 62 district general hospitals should have a second cardiologist, but only 12 of them do. This indicates an additional need for 50 posts.

The need for additional physicians within cardiac centres is more difficult to determine, but an approximation can be made by quantifying the need for investigations and treatment in relation to cardiac surgery, which forms the major part of the present workload. The recommendation for the annual need for cardiac surgery is 400–500 per million population.[12] The population of England and Wales is a little over 50 million, implying (taking the mid point) that 22 500 operations should be carried out each year. If every surgeon does 250 operations, and if twice as many cardiologists are needed as surgeons—figures that are widely accepted—then we require at least 180 adult cardiologists in the centres, compared with the present total of 117. This estimate of a requirement for 63 additional cardiologists within major centres is a conservative figure that does not allow for the new demands of angioplasty and added responsibilities in other

Table 18 Non-invasive cardiac facilities (number of HDs with given facility) by Region in England and Wales at 1 March 1989 (for populations see table 17) (1984 data are shown in parentheses)

	Echocardiography					*Ambulatory monitoring*			
Region	*M mode only*	*Cross sectional*	*Doppler*	*Colour flow*	*Scintigraphy*	*Recording*	*Analysis*	*Stress tests*	*Coronary Ambulance*
East Anglia	(3)	8 (5)	5		4	8 (8)	6 (4)	8 (8)	2 (1)
Mersey	3 (1)	6 (2)	5	2	1	10 (7)	8 (5)	10 (9)	5 (1)
North East Thames	(3)	16 (10)	11	5	9	16 (15)	14 (14)	16 (16)	2 (1)
North West Thames*	1	10 (8)	7	5	8	12 (15)	11 (12)	12 (13)	1
North Western	3 (2)	16 (10)	10	5	8	18 (17)	18 (15)	18 (17)	7 (3)
Northern	3 (4)	10 (7)	10	4	9	16 (16)	9 (6)	16 (15)	13 (1)
Oxford	(3)	8 (3)	6	2	2	8 (7)	8 (7)	7 (7)	7 (1)
South East Thames	2 (2)	13 (8)	10	3	9	15 (15)	15 (14)	15 (15)	3 (3)
South West Thames	1 (4)	12 (5)	8	4	4	13 (13)	10 (10)	13 (13)	9 (4)
South Western	1	9 (8)	8	7	9	11 (11)	8 (9)	10 (10)	7 (4)
Trent	(3)	9 (5)	6	1	10	12 (9)	10 (7)	12 (10)	6 (2)
Wessex	1 (3)	8 (3)	6	1	4	10 (10)	8 (5)	9 (9)	5 (3)
West Midlands	4 (5)	16 (9)	10	4	15	22 (21)	18 (14)	19 (18)	9 (2)
Yorkshire	5 (1)	12 (8)	10	5	8	15 (15)	12 (13)	15 (15)	7 (2)
Wales‡	1 (2)	8 (6)	7	2	6	8 (8)	8 (8)	8 (8)	7 (1)
Special hospitals		4 (4)	3	2	4	4 (4)	4 (4)	4 (4)	
Totals	25 (36)	165 (101)	122‡	52‡	110‡	198 (191)	167 (147)	192 (187)	90 (29)

* Hammersmith now shown under special hospitals.
† Wales has 18 district hospitals.
‡ Data for 1984 were not available for comparison in these three categories.

spheres. We may also be paying inadequate attention to the radiation hazards faced by the new generation of interventionalist cardiologists, especially if fewer registrars are available for the less demanding routine catheter investigations.

Implications of the shortfall in consultant staffing

In England and Wales there are at present 323 consultant cardiologists according to the 1990 biennial survey. The total shortfall, set out in detail above, is:

Additional cardiologists for centres	63
Cardiologist for districts with none	44
Cardiologists (2) for bigger districts	50

Thus we have a pressing need for 157 posts, to make a total of 478—an increase of almost exactly 50% on the current figure.

The present staffing levels are clearly inadequate for the needs of the service and the present annual growth rate in consultant posts (approximately 4·5%) is now equivalent to 14 posts per year. If this trend continues over the next decade we will have met most of the shortfall outlined above—that is, 140 of the 159 posts that we believe are urgently needed now. The guidelines, however, may have shifted by then. The calculations we have used assume that the service workload will continue to be met mostly by trainees. An equitable distribution of resources at an acceptable level plus the objective of a consultant based service, however, can be achieved in cardiology by the beginning of the 21st century only if the annual growth rate in consultant posts is appreciably greater than the current 4·5%.

A rapid rate of growth cannot be achieved easily. The logical approach would be to create first the appropriate number of training posts and then increase consultant posts as more trainees become available. This would be unacceptable, however, without the guarantee of a subsequent and commensurate increase in consultant posts; and no such guarantee could be given. We should therefore increase the number of consultant posts and training posts concurrently, and accept the short term expedient of premature promotion—as indeed is occurring already owing to the present shortage of senior registrars.

We drew attention in our previous survey to the remarkable difference in the provision of cardiology between the United Kingdom and most of the rest of the developed world.[4] Even now we have only 6·4 cardiologists per million population in England and Wales. Our 1989 paper quoted the ratio for Europe as a whole as 45 per million, with the recommended figure for the United States being 60 per million. We see little prospect of provision in the United Kingdom on a scale similar to that which is regarded as satisfactory in many neighbouring European countries.

Our present requirement for posts at senior registrar level depends on predictions of consultant vacancies in three or four years time. We can offer predictions based on planned retirement dates, present expansion, and an allowance for unexpected events such as death. To this we should add numbers for a greater rate of expansion as argued above, but the data presented in figure 2 (based on retirement plans) show a step-wise increase in numbers that are needed from 1997, even without a greater rate of growth. The JPAC formula does not permit any account to be taken of such predictions, even when it is based on carefully collected data. The present tendency for premature appointments from senior registrar to the consultant grade therefore seems destined to recur—after a brief lull—to a greater extent than ever before. This undesirable situation has already affected paediatric cardiology and could be prevented by planning that is not constrained by the rigid application of inappropriate formulae. The reduction of the training period from four to three years in our new programme[5] will mitigate but not prevent a future crisis.

We thank our colleagues who completed our questionnaires so diligently. We seek their continuing forbearance.

1 Chamberlain DA, Goodwin JF, Emanuel RW, Bailey LG. Career prospects in cardiology in England and Wales. Survey of 15 health regions. *Br Heart J* 1981;45:460–3.
2 Chamberlain D, Bailey L, Emanuel R, Oliver M. Staffing and facilities in cardiology in England and Wales July 1982. Second biennial survey. *Br Heart J* 1985,50: 597–604.
3 Chamberlain D, Bailey L, Julian D. Staffing and facilities in cardiology in the United Kingdom 1984 Third biennial survey. *Br Heart J* 1986,55.311–20.
4 Chamberlain D, Bailey L, Sowton E, Ballantyne D, Boyle D McC, Oliver M. Staffing in cardiology in the United Kingdom 1988. Fifth biennial survey. *Br Heart J* 1989; 62 482–7.
5 Chamberlain D, Julian D, Sleight P, Sowton E Proposals for a new training programme for cardiology *Br Heart J* 1990;63:317–20.
6 Chamberlain D. Staffing in cardiology in the United Kingdom 1988. Fifth biennial survey [letter]. *Br Heart J* 1990,63:262.
7 Medical Manpower and Education Division, Department of Health. Medical and dental staffing prospects in the NHS in England and Wales 1989 *Health Trends* 1990,3:96–103.
8 Report of a working group of the British Cardiac Society. Cardiology in the district hospital. *Br Heart J* 1987; 58:537–46.
9 British Cardiac Society. Working Party Report on Cardiac Rehabilitation. *Br Heart J* unpublished
10 The Modern Ambulance Service Good Practice Guidance. Report by Working Group to Chief Executives NHS Management Executives. November 1990.
11 Provision of services for the diagnosis and treatment of heart disease in England and Wales. Third Report of a Joint Cardiology Committee. Royal College of Physicians of London and the Royal College of Surgeons of England. *Br Heart J* 1985;53·477–82.
12 Provision of services for the diagnosis and treatment of heart disease Fourth report of a Joint Cardiology Committee of the Royal College of Physicians of London and the Royal College of Surgeons of England. *Br Heart J* (In press).

LETTERS TO THE EDITOR

- *The British Heart Journal welcomes letters commenting on papers that it has published within the past six months.*
- *All letters must be typed with double spacing and signed by all authors.*
- *No letter should be more than 600 words.*
- *In general, no letter should contain more than six references (also typed with double spacing).*

Endothelium in control

SIR,—In his St Cyres Lecture (*British Heart Journal* 1991;65:116–25) Professor A H Henderson states that the half life of endothelium derived relaxing factor (EDRF) nitric oxide is "likely to be less than a second in vivo" and that "each millimetre of endothelium controls its little bit of the vascular system." I believe it is possible to place these suggestions on a more precise basis. In the picomolar concentrations of nitric oxide secreted by endothelium the half life of the reaction between nitric oxide and oxygen is far too slow to account for this proposed rapid removal.[1] By contrast the rate of removal by haem groups is exceedingly rapid and the second order rate constant for reaction of nitric oxide with the red cell is 167 $l\ mmol^{-1}\ s^{-1}$ in vitro.[2] There is growing evidence that this value may be applied to blood nitric oxide uptake in vivo at least in human pulmonary capillary.[3] Though the rate of reaction of nitric oxide with oxyhaemoglobin in vitro[4] is about 250 times as fast as the reaction with the red cell, because less than 0·03% of the haemoglobin in blood is in the free form, the reaction with the red cell is quantitatively more important. Similar arguments apply to tissue haem groups and also superoxide ion. The half life of nitric oxide in blood is obtained as follows:

$$t½ = 0·693/(167 \times 9) = 4·6 \times 10^{-4} \text{ seconds}$$

where 0·693 is ln 2, 167 is the second order rate constant (see above), and 9 is the concentration of Hb in mmol/l corresponding to a haemoglobin concentration of 14 6 g/dl. The distance travelled in one half life is obtained as the velocity of blood flow (1 m/s in the aorta during systole, 0·3 m/s in the vena cava, 5 10^{-4} m/s in a capillary[5]) multiplied by t½: that is, 4 6 × 10^{-4} m in the aorta, 1·4 × 10^{-4} m in the vena cava, and 2 × 10^{-7} m in capillary. The half life of nitric oxide in vivo in blood can be seen to be exceedingly short and the distance "downstream" over which a section of endothelium can have an influence extremely small especially in the capillary.

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1 Austin AT. The chemistry of the higher oxides of nitrogen as related to the manufacture, storage and administration of nitrous oxide. *Br J Anaesth* 1967,39:345–9.
2 Carlsen E, Comroe JH Jr The rate of uptake of carbon monoxide and of nitric oxide by normal human erythrocytes and experimentally produced spherocytes. *J Gen Physiol* 1958; 42:83–107.
3 Borland C NO and CO transfer *Eur Respir J* 1990;3.977–8
4 Doyle MP, Hoekstra JW. Oxidation of nitrogen oxides by bound dioxygen in haemoproteins. *J Inorg Biochem* 1981;14:351–8.
5 Horrobin DF. *Medical physiology and biochemistry*. London: Edward Arnold, 1968: 307–9.

This letter was shown to the author, who replies as follows:

SIR,—I am grateful to Dr Borland for his interest and for the quantitative pyramid he builds on my point which was simply to emphasise the very localised nature of vasodilatation mediated by EDRF.

The half life of EDRF was documented as beng in the order of seconds by bioassay of oxygenated effluent buffer from endothelialised artery segments.[1] Nitric oxide oxidation in aqueous buffer is related to po_2 but is some 30 times faster in transit through perfused hearts where its half life was shown to be about 0·1 s.[2] This is consistent with previously reported evidence that the intraluminal dilator signal in the anaesthetised dog femoral artery is localised to within 1 cm.[3] Clearly the presence of haemoglobin (which has about 1500 times greater affinity for nitric oxide than for carbon monoxide) will further reduce the half life of nitric oxide within the vascular compartment in vivo. Small amounts of "free" haemoglobin are in fact complexed to haptoglobin in circulating blood (<0·03% of total haemoglobin in the blood, as Dr Borland states), accounting for the variable EDRF-inhibiting activity of plasma (the inhibitory activity in samples from some of our human volunteers was unusually high, and after appropriate experimentation, this was attributed to alcohol intake).[4] The largest sink of haemoglobin is indeed within the erythrocytes, whose EDRF inhibitory activity we found to be that of similar concentrations of free haemoglobin,[5] as expected from the lipid solubility of nitric oxide and its ready passage through red cell membranes. Superoxide anions, widely present in biological systems, further shorten the half life of nitric oxide[6] (rate constant of the reaction $NO + O_2^-$ at physiological pH, $k = 3·7 \times 10^7\ M^{-1}s^{-1}$). The concentration of oxygen free radicals is likely to vary widely, particularly under pathological conditions. Recent evidence suggests, for example, that the reduced EDRF activity shown in experimental hypercholesterolaemia may be due to EDRF inactivation rather than decreased production, on the basis of a decrease in bioassayed dilator activity but an increase in nitric oxide production when measured by chemiluminescence,[7] the decrease in activity being attributable possibly to increased superoxide anion production beneath atheromatous plaques.[8]

Biology, let alone pathology (and perhaps alcohol) clearly introduces complexity. I think we agree though that locally released EDRF has little downstream activity.

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1 Griffith TM, Henderson AH, Hughes Edwards D, Lewis MJ Isolated perfused rabbit coronary artery and aortic strip preparations: the role of endothelium-derived relaxant factor. *J Physiol (Lond)* 1984;351:13–24.
2 Kelm M, Schrader J. Control of coronary vascular tone by nitric oxide *Circ Res* 1990; 66:1561–75.
3 Angus JA, Campbell GR, Cocks TM, Manderson JA. Vasodilatation by acetylcholine is endothelium-dependent. a study by sonomicrometry in canine femoral artery *in vivo* *J Physiol (Lond)* 1983;344.209–22.
4 Edwards DH, Griffith TM, Ryley HC, Henderson AH. Haptoglobin-haemoglobin complex in human plasma inhibits endothelium-dependent relaxation: evidence that endothelium derived relaxing factor acts as a local autocoid. *Cardiovasc Res* 1986;20 549–56.
5 Evans HG, Ryley HC, Hallett I, Lewis MJ. Human red blood cells inhibit endothelium-derived relaxing factor (EDRF) activity *Eur J Pharmacol* 1989;163:361–4.
6 Gryglewski RJ, Palmer RMJ, Moncada S. Superoxide is involved in the breakdown of endothelium-derived vascular relaxing factor. *Nature* 1986;320:454–6.
7 Minor RL, Myers PR, Guerra R, *et al.* Diet-induced atherosclerosis increases the release of nitrogen oxides from rabbit aorta. *J Clin Invest* 1990;86.2109–2116.
8 Nakamura M, Tagawa H, Tomoike H. Reduced release of EDRF and significant inactivation of EDRF at the tunica media beneath the atheromatous plaque in aortas of WHHL rabbits [abstract] *Arch Int Pharmacodyn* 1990, 305:209.

Novel exercise protocol suitable for use on a treadmill or a bicycle ergometer

SIR,—The standardisation of exercise tests is now a major issue and the Working Group on Exercise Testing of the European Society of Cardiology has organised a committee to examine this problem. In November 1990 Dr Northridge and colleagues (*British Heart Journal* 1990,64:313–6) presented data on a new exercise protocol that is based on exponential (rather than linear) increments in workload. In their experience the rise in oxygen consumption (ml/kg/min) is very similar whether the test is performed on a bicycle or on a treadmill; alto they mention that the highest stage required to test even relatively fit patients is reached after 15 minutes.

We have tested prospectively and randomly these new protocols in 13 healthy men (mean age 33, range 25–49; mean weight 80, range 62–115 kg) and our data (fig 1) indicate that oxygen consumption was significantly greater (unpaired *t* test; $p < 0\ 05$) during the last nine minutes of the bicycle standardised exponential exercise protocol (STEEP). The heart rates were also greater ($p < 0·05$) with the bicycle protocol during the last six minutes of the exercise test (fig 2). All the subjects were able to perform the 15 minutes of the STEEP treadmill test while only six were able to reach the fifteenth minute of the bicycle protocol; at the fifteenth minute of the STEEP bicycle test, all patients complained of pain in the legs, a symptom that was almost absent at the fifteenth minute of the STEEP treadmill test. Also the reason for interrupting the STEEP bicycle test was always leg muscle fatigue or pain. These observations about heart rate and exercise duration are very similar to those made by Northridge *et al.*

The explanation for our different results remains unclear. In our experience, we think that for the heaviest subjects the final increases in workload of the bicycle protocol are too large (from 25 to 40 w/min) to be tolerated by the leg muscles and that muscle soreness becomes the major limiting factor. Because of the differences in oxygen consumption and in exercise duration, we think that these new STEEP tests are not the answer to our growing need for standardised exercise tests that can be used on both the treadmill and the bicycle ergometer. Also we feel that the very slow rise in oxygen consumption seen during the first six minutes of both STEEP tests make them an unsatisfactory basis for the extrapolation of maximal oxygen uptake from maximal workload and for measuring the subtle changes observed after a given treatment. Before being tested in patients, these new protocols should be extensively tested in healthy volunteers and compared with other exercise protocols.

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This letter was shown to the authors, who reply as follows:

Sir,—The data presented by Dr Essamri and colleagues in 13 male volunteers confirm many of our findings with the STEEP exercise test. There are, however, some important differences that may be explained, at least in part, by methodological considerations. It is likely that young men living in Belgium are more accustomed to cycling than our Glaswegian volunteers and this may explain why they are able to perform more aerobic work on a bicycle ergometer. Furthermore, the significance levels quoted were obtained using unpaired *t* tests, such that for the final stages the six fittest subjects who were able to complete the bicycle protocol were compared with the whole group who completed the treadmill protocol. It is not surprising that the six fittest subjects had a higher mean oxygen consumption than the group as a whole. It would be more appropriate to use a paired test, such that data from subjects completing a given stage of one protocol are compared only with data from the same subjects during the other protocol.

We are encouraged that Dr Essamri and colleagues agree with the need for standardisation of exercise testing within Europe—but which protocol are we to use as a standard? The STEEP protocol has several advantages over existing protocols, including short stages (as recommended by Buchfuhrer *et al*[1]), suitability for both treadmill and bicycle testing, adjustment for body weight during the bicycle protocol so that subjects of different size exercise at similar relative intensity at each stage, and exponential increments in workload making the test applicable to a very wide range of patients. None of these improvements over existing protocols is contested in the letter from Essamri *et al*. They have, however, demonstrated a difference in oxygen consumption during the later stages of the treadmill and bicycle protocols, which may indicate a need for a minor modification of one or other protocol. However, we did not suggest that the two tests were identical, only that they were comparable. Bicycle and treadmill testing have certain fundamental differences—which were discussed in our original report. The STEEP tests merely offer a pragmatic solution to the problem of standardisation when some laboratories use treadmills while others use bicycle ergometers.

Their assertion that the final workload increments are too large in heavy subjects is clearly unwarranted because the whole point of adjustment for body weight is that all subjects experience the same relative workloads and increments. In fact the data of Essamri *et al* confirm this principle because the standard deviations of the mean oxygen consumption for each stage of the bicycle protocol (assuming that their figure shows standard deviations rather than standard errors) are very small even though the study included a remarkable range of body weights—from 62 kg to 115 kg. We fully agree that the STEEP protocol is not suitable for inferring maximal oxygen uptake from maximal workload in patients with cardiovascular disease—but this is not recommended for any protocol.[2,3]

Finally, we think that firm conclusions cannot be reached until new standard exercise protocols, such as the STEEP test, are validated in suitable patient populations.

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1 Buchfuhrer MJ, Hansen JE, Robinson TE, Sue DY, Wasserman K, Whip BJ. Optimising the exercise protocol for cardiopulmonary assessment. *J Appl Physiol* 1983;55:1558–64
2 Ragg KE, Murray TF, Karbonit LM, Jump DA. Errors in predicting functional capacity from a treadmill exercise stress test. *Am Heart J* 1980;100.581–3
3 Myers J, Froelicher VF Optimising the exercise test for pharmacological investigations. *Circulation* 1990,82 1839–46.

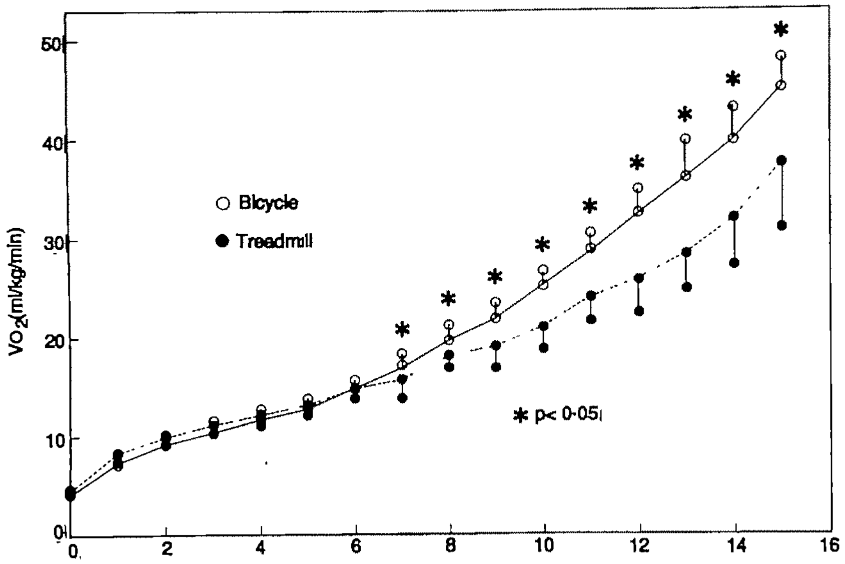

Figure 1 Oxygen consumption.

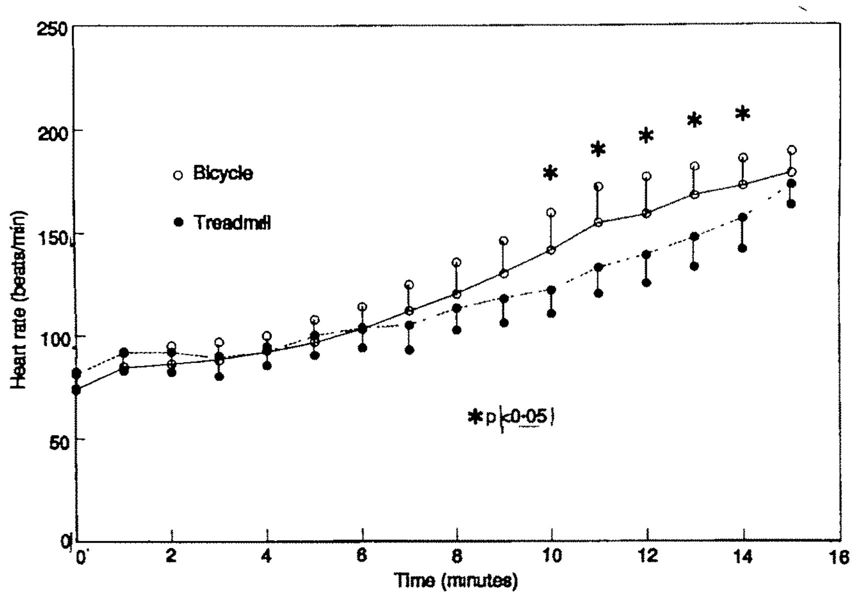

Figure 2 Heart rate.

Fatal aortic rupture during balloon dilatation of recoarctation

Sir,—I read the paper by Balaji (*British Heart Journal* 1991;65:100–1) with interest. They reported aortic rupture and death in an eight year old child after balloon angioplasty for aortic recoarctation that developed after patch angioplasty procedure. We have had extensive experience with balloon angioplasty of aortic coarctations, both native and postoperative,[1-9] and have not observed a similar complication. We do not agree with Balaji *et al* that balloon angioplasty should be avoided in cases of recoarctations after patch angioplasty. The complication reported in Balaji *et al* is a problem related to the technique of angioplasty that they adopted.

Firstly, I do not believe that balloon angioplasty should be performed without monitoring the pressure in the balloon. The purpose of monitoring the pressure is not to prevent overinflation (as they seem to imply) but to prevent rupture of the balloon. I believe that balloon rupture should be prevented at all cost, not only to avoid complications such as that reported by Balaji, but also to prevent arterial injury, which is more likely during the removal of a ruptured balloon.

Second, I do not understand the purpose of attempting to redilate with a 12 mm balloon after a previous dilatation with a 15 mm balloon.

Third, the Olbert catheter system that Balaji *et al* used in this case produces longitudinal movement of the balloon material over the internal surface of the aorta and is likely to injure the aorta further.

Based on our experience[1-9] and that reported by Cooper *et al*[10] and Hellenbrand *et al*[11] we believe that aortic recoarctations that develop after all types of coarctation surgery—namely, end-to-end anastomosis after resection, subclavian flap angioplasty, patch angioplasty (Dacron, Gore-Tex, or pericardial patch), and interrupted aortic arch repair—can be successfully dilated.

To prevent aortic rupture and/or subsequent aneurysms it is vital to avoid manipulation of the tips of the guide wire and catheters in the region of freshly dilated coarctation and to avoid using a balloon that is larger than the descending aortic diameter at the level of the diaphragm.

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This letter was shown to the authors, who reply as follows:

SIR,—We thank Dr Rao for his helpful comments. However, we do not agree with some of them. Dr Rao has reported seven cases of angioplasty for recoarctation[5] without giving any patient details, particularly about the nature of their previous surgery. All the other reports[1-9] from his group deal with native coarctation in 30 cases, a lesion in which the method of action of balloon angioplasty may be very different to that in recoarctation.

The results of Cooper *et al*[10] that Dr Rao quotes to support his conclusions come from our hospital. Until the aortic rupture that we reported,[1] our experience with angioplasty for recoarctation was very promising indeed. Our chief aim in drawing attention to this case was to introduce a note of caution. As we indicated in the case report, there are few reported cases of angioplasty in patients who have previously undergone patch aortoplasty. Most workers including Dr Rao have not reported details of the previous surgery that the patients had undergone. We cited, however, the large and successful experience from the Boston group in patients who had had patch repair.

We accept we should avoid balloon rupture and now suggest pressure monitoring of the balloon is used. We chose to use the smaller Olbert balloon because we believed that it was firmer than the larger Meditech balloon, which had had no "apparent" effect on the coarctation.

In our experience longitudinal balloon movement is equally likely with all balloon catheters. Perhaps what is more important is the straightening effect of the balloon within a curved structure such as the aorta. It is our long-standing practice not to manipulate guide wires or catheter tips across freshly dilated coarctations.

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1 Rao PS Transcatheter treatment of pulmonary stenosis and coarctation of the aorta· experience with percutaneous balloon dilatation. *Br Heart J* 1986;56.250–8.
2 Rao PS. Balloon angioplasty for coarctation of the aorta in infancy. *J Pediatr* 1987;110.713–8.
3 Rao PS, Najjar HN, Mardini MK, Solymar L, Thapar MK. Balloon angioplasty for coarctation of the aorta: immediate and long-term results. *Am Heart J* 1988;115:657–65.
4 Rao PS, Thapar MK, Kutayli F, Carey P. Causes of recoarctation following balloon angioplasty of unoperated aortic coarctations. *J Am Coll Cardiol* 1989;13·109–15.
5 Rao PS. Which coarctations should we balloon dilate? *Am Heart J* 1989;117:787–9.
6 Rao PS, Carey P. Remodelling of the aorta following successful balloon coarctation angioplasty. *J Am Coll Cardiol* 1989;14. 1312–7.
7 Rao PS. Balloon angioplasty of aortic coarctation: a review *Clin Cardiol* 1989,12:618–28.
8 Rao PS, Thapar MK, Galal O, Wilson AD. Follow up results of balloon angioplasty of native coarctation in neonates and infants. *Am Heart J* 1990;120·1310–5.
9 Rao PS, Wilson AD, Chopra PS. Immediate and follow-up results of balloon angioplasty of postoperative recoarctation in infants and children. *Am Heart J* 1990;120:1315–20.
10 Cooper SG, Sullivan ID, Wren C. Treatment of recoarctation balloon dilatation angioplasty. *J Am Coll Cardiol* 1989;14·413–9.
11 Hellenbrand WE, Allen HD, Golinko RJ, Hagler DJ, Lutin W, Kan J Balloon angioplasty for aortic recoarctation. results of Valvuloplasty and Angioplasty of Congenital Anomalies Registry. *Am J Cardiol* 1990;65 793–7.

BOOK REVIEW

Principles and practice of cardiovascular imaging. Edited by G M Pohost and R A O'Rourke. (Pp 942; £115.) Boston, Toronto, London: Little, Brown & Company, 1991. ISBN 0-316-71247-7.

The practice of modern cardiology requires extensive use of imaging. The everyday value of echocardiography and angiography in routine diagnosis has made the cardiologist a provider as well as a user of imaging. Though many present day cardiologists have contributed to the development of new imaging techniques it is still difficult to keep up to date with all aspects of imaging and to be sure of its rational use. Trainee cardiologists have an even more difficult task because they need to understand the principles and practice of a wide range of imaging techniques, all of which have an extensive literature. This book, in drawing together under one cover all the common methods used, including the uses of echocardiography, radionuclides, *x* ray, and magnetic resonance imaging, brings partial salvation.

The book is organised into three sections: the first deals with the technology of each imaging method, the second with the clinical applications, and the third with cost considerations. The first and largest section is the most rewarding, with the basic principles of physics, safety, and protection preceding the clinical use of each technique. Despite the multiauthor approach each section is balanced, and the writing is clear and crisp and extensively referenced—though there is a tendency to ignore work published in non-American journals. No doubt for cost reasons the colour plates are aggregated together at page 749 but this is not clearly signalled in the section on colour flow Doppler mapping (pp 136–145). It seems a pity that the colour plates were not incorporated into this chapter.

I had looked forward to reading the second section which sets out to show how the technologies should be used to solve common clinical problems rather than what they can do. I found this section disappointing, however. Again it tended to show what could be done rather what was needed to make the diagnosis. Separate chapters that cover echocardiography and radionuclides in the investigation of cardiac muscle disease without bringing in the possible use of magnetic resonance imaging illustrate a divided rather than an integrated approach. The style of this section is also more uneven, with some authors taking a more clinical approach than others. The illustrative cases in the section on valvar heart disease by Kotlewski and Rahimtoola seem to have caught the spirit of the section better than others. In all, the section seems better in conception than in execution.

National Health Service funding for imaging equipment has always been difficult but cost considerations are becoming increasingly important. We are still some way removed from a prospective payment system based on diagnostic-related groups (DRGs) but medicine does seem to be marching in this direction. The final section of the book gives an excellent account of the North American experience and tackles important issues such as the impact of imaging on the health care system and the implications for the future. This section is mandatory reading for anyone managing imaging services.

Despite reservations about the middle section this book is a valuable guide to the use of imaging. It should be read by all trainees and referred to frequently by all users and providers of cardiac imaging services

ALEXANDER L MUIR

The title reviewed here is available from the BMJ Bookshop, PO Box 295, London WC1H 9TE. Prices include postage in the UK and for members of the British Forces Overseas, but overseas customers should add 15% to the valoue of the order for postage and packing. Payment can be made by cheque in sterling drawn on a UK bank, or by credit card (MasterCard, VISA, or American Express) stating card number, expiry date, and your full name.

NOTICES

1992

The Annual Meeting of the **British Cardiac Society** will take place at the Harrogate International Centre on 26 to 29 May. The closing date for receipt of abstracts will be 3 January.

The 3rd International Conference on **Cardiac Doppler-Echo and Color Flow Imaging** will be held in Dubrovnik on 31 May to 3 June: ICCD, Dr Nikša Drinković, Department of Cardiovascular Diseases, University Hospital Centre Rebro, Kišpatićeva 12, 41000 Zagreb, Yugoslovia (Fax: 41 420-793. Tel: 041/434-444, 435-555).

BRITISH CARDIAC SOCIETY NEWSLETTER

During a recent meeting at the Medical Devices Directorate at the Department of Health, we became aware of a problem that will be of interest to cardiologists who are active in the field of resuscitation. It concerns battery packs for portable defibrillators. Some hospitals and ambulance stations use battery packs that are not supplied by the defibrillator manufacturer because this is a cheaper option. It is not always a wise one, however. Some batteries from alternative sources have poor performance characteristics that have resulted in investigations of apparent defibrillator defects and the issue of Safety Action Bulletins. The Department of Health has told us that tests of unauthorised battery packs showed significant overheating during successive 360 J charges leading to a loss in capacity, a longer time than is specified for charging, and a reduced number of shocks per full battery charge. Readers should know that manufacturers classify the battery pack of a defibrillator as a critical component in their agreements under the agreed quality document (Good Manufacturing Practice for Medical Equipment). The quality and form of the design of defibrillator batteries, the inspections, quality testing, and traceability all make legitimate additions to the cost of this high specification equipment that may not be necessary or appropriate for battery packs intended for less demanding or critical use. We should add that some alternative battery suppliers are now in the process in installing quality systems that would satisfy the department and may in time be recognised by the NHS in its purchasing policy. But considerable responsibility is placed with the user who elects to use substitute batteries and we suggest that suppliers be requested to demonstrate and perhaps give a written undertaking that their design allows equivalent performance to that in batteries supplied by the manufacturer of the defibrillator.

The recent distribution of the current list of British Cardiac Society committees and their membership has drawn the comment that the same names do seem to recur with undue frequency. To this we plead guilty. The society has officers who number four or five (the President elect is a post sometimes filled and sometimes not). We do believe it is essential to have at least two officers on every committee to ensure that we act cohesively. Officers do not seek to dominate committees—though some have additional influence because they are chairmen. Perhaps it is also fair to mention that before we had our new committee structure, all decisions were necessarily made by the officers, by council, and at general meetings by the membership. If we now have an additional way for members who are not on Council to have influence in areas of their interest or expertise, this should not be seen as a move away from democracy. But two issues need to be addressed. The first is how to identify members who seek this sort of involvement: we often find it difficult to persuade colleagues to take on new responsibilities that can be time consuming and even difficult to arrange in these days of stricter contracts. Please tell us if you have an interest in any of the committees and would be willing to serve. The second related issue is how to make decisions on representation on the committees, having regard to the need for balance: we always consider the balance between London and out-of-London, between North and South (and, to the West, Ireland), between younger and older, between academic and NHS, between the centres and the district general hospitals, and between adult and paediatric cardiology. Clearly we cannot achieve a satisfactory mix on committees with limited membership, but the balance could easily become less satisfactory. For this reason we have taken the view that council are elected, and that the composition of committees should be left to them—but with influence from the wider membership always welcome. Is this reasonable?

Readers will know we are anxious to promote opportunities for part time training in cardiology. The BMA have arranged a seminar for any junior doctors interested in part time training. It will be held in the Roben Suite at Guy's Hospital at 6.30 pm (for 7.30 pm) on 11 November. Further information can be obtained from David Barr on 081-660 5558.

Attilio Maseri has now left the Royal Postgraduate Medical School to take up a new appointment in Italy. His influence has been great, and we cannot let his departure pass without comment. John Goodwin has written the appreciation that follows.

"Attilio Maseri became the British Heart Foundation Sir John McMichael Professor of Cardiovascular Medicine at the Royal Postgraduate Medical School in 1979. His previous career was distinguished. Training in Padua, in Pisa, and in the United States (Columbia and John's Hopkins) had equipped him for a career in research in nuclear cardiology and coronary artery disease. By 1969, he was head of the coronary research group in the laboratory of clinical physiology of the National Research Council in Pisa, and the following year became the Professor of Cardiopulmonary Pathophysiology. His chief interests were in radionuclide studies of myocardial blood flow, regional myocardial perfusion and metabolism, and the pathogenetic mechanisms of acute myocardial infarction. But he was best known for his original studies in coronary artery spasm. Later, while at the Royal Postgraduate Medical School, he extended his range to include mechanisms of coronary occlusion in acute myocardial infarction with colleagues in cardiology, and to the role of neuropeptide and other transmitters in the control of the circulation, in collaboration with Stephen Bloom and Julia Pollak.

Attilio brought to Hammersmith Hospital a cool critical look at basic mechanisms that was most refreshing. The Royal Postgraduate Medical School has always eagerly welcomed exciting new talent from outside Britain, and Attilio has been a prime example.

As the second Professor of Cardiology in the United Kingdom and the first at the Royal Postgraduate Medical School, I welcomed the new professorial blood with enthusiasm. It was a pleasure to work with him in the realm of teaching. Together we set up the first diploma course in cardiology, loyally aided by many colleagues. Attilio's specialist courses in cardiology, often held in association with other institutions such as the European Society of Cardiology and the American College of Cardiology, were highly successful and attracted many well known international speakers in addition to large enthusiastic audiences.

While at Hammersmith, he gave a number of notable named lectures in the United Kingdom, the United States, Europe, and Japan, and became a member of many important scientific councils such as the National Italian Research Council and the Council on Thrombosis of the International Society and Federation of Cardiology. In addition to many other professional awards and titles, Attilio will be well remembered at Hammersmith Hospital for his and Francesca's generous hospitality in their home.

I have appreciated Attilio as a charming, helpful, and enthusiastic colleague. He takes the best wishes of us all with him to his important new appointments as Professor of Cardiology in the Catholic University of Rome and Director of the Institute of Cardiology, Polyclinico Agostino Gamelli. We hope he will keep in regular touch and visit often."

John Goodwin's appreciation is warmly endorsed by all of us.

This issue of the *British Heart Journal* contains the Sixth Biennial Survey on Staffing and Facilities in Cardiology in the UK (1990). Readers will no doubt study all the data carefully. It may be worth drawing your attention to the fact that there are still 44 districts in England and Wales with no cardiologist or only an occasional visiting cardiologist. We perceive an overall requirement for over 150 more consultant cardiologists to meet existing needs, but even the present rate of expansion is going to lead to a dearth of senior registrars in the last few years of this decade. Although these data are available and irrefutable, the formula for adjusting the number of senior registrar appointments (Joint Planning Advisory Committee) does not permit any expansion to meet this need. Unless the ground rules are changed, we are heading for a crisis.

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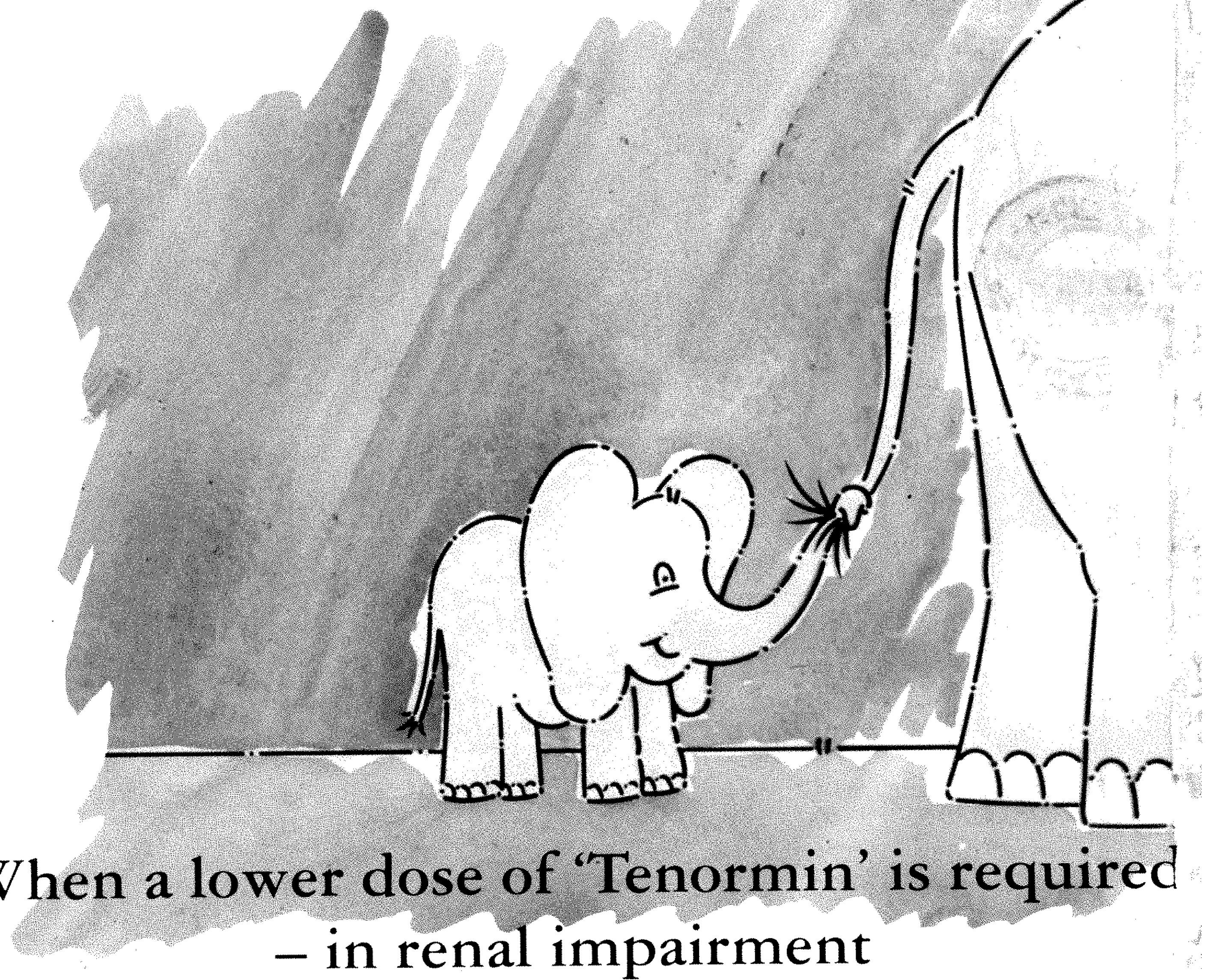

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